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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No. 6,441,168:

Issued: August 27, 2002

Inventors: Rüdolf Muller,
Rudolf Moser, and
Thomas Egger.

Assignee: Eprova AG

Title: Stable crystalline salts of 5-methyltetrahydrofolic acid

Mail Stop: Hatch-Waxman PTE
Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

APPLICATION FOR EXTENSION OF
TERM UNDER 35 U.S.C. §156

SIR:

Applicant, Eprova AG, a corporation organized and existing under and by virtue of the laws of Switzerland, and having a principal place of business at Im Laternenacker 5, CH-8200 Schaffhausen, Switzerland, represents that it is the assignee of record of the entire interest in and to letters patent of the United States No. 6,441,168 granted to Rüdolf Muller, Rudolf Moser, and Thomas Egger on August 27, 2002, for "Stable crystalline salts of 5-methyltetrahydrofolic acid." An assignment of said patent from Rüdolf Muller, Rudolf Moser, and Thomas Egger to Eprova AG was recorded in the U.S. Patent and Trademark Office on August 21, 2000 at Reel 011055/ Frame 0009.

As of April 1, 2010, Eprova AG merged with Merck & Cie, located in Altdorf, Switzerland. The new name of the company is Merck & Cie, having a principal place of business at Im Laternenacker 5, CH-8200 Schaffhausen, Switzerland. Documents for recordation of the merger will be filed with the USPTO in the near future.

BEYAZ™ is an oral contraceptive (COC) which contains drospirenone, ethinyl estradiol, and levomefolate calcium (polymorph Form I) as active ingredients. The dosing

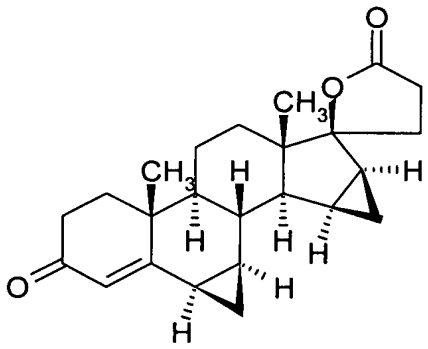
Attorney Docket No. BAYSCH-290-X

regimen is made up of blister packs each of which contains 28 film-coated, biconvex tablets wherein 24 tablets contain drospirenone, ethinyl estradiol, and levomefolate calcium (polymorph Form I) as active ingredients, and 4 tablets contain only levomefolate calcium (polymorph Form I) as the active ingredient. Levomefolate calcium (polymorph Form I) and a method of producing levomefolate calcium (polymorph Form I) fall within the ambit of claims of U.S. Patent 6,441,168. Bayer Schering Pharma Aktiengesellschaft was granted approval by the Food and Drug Administration for commercial marketing or use of BEYAZ™ on September 24, 2010. Bayer Schering Pharma Aktiengesellschaft has a license under U.S. Patent 6,441,168 from Eprova AG.

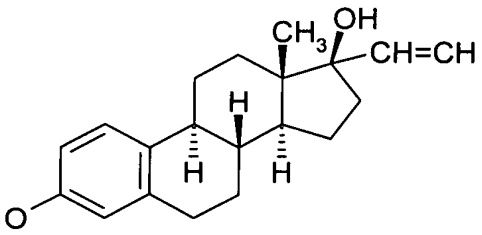
Applicant, acting through its duly authorized attorney, hereby submits this application for extension of patent term under 35 U.S.C. §156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. §1.710-1.785). For the convenience of the U.S. Patent and Trademark Office, the information presented in this application is in a format which follows the requirements of 37 C.F.R. §1.740(a).

(1) The approved product, BEYAZ™, contains a series of tablets wherein each tablet: (1) contains drospirenone, ethinyl estradiol, and levomefolate calcium (polymorph Form I) as the active ingredients, or (2) contains levomefolate calcium (polymorph Form I) as the sole active ingredient.

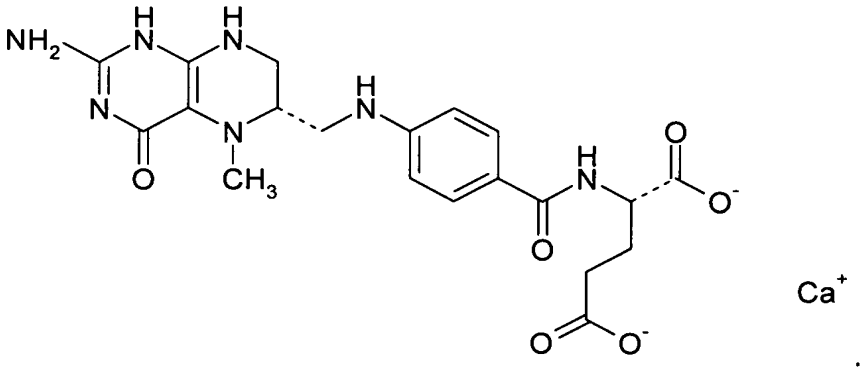
Drospirenone is a synthetic progestational compound which has the chemical name of 6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11, 12,13,14,15,15a,16-hexadecahydro10,13-dimethylspiro-[17H-dicyclopropa- [6,7:15,16]-cyclopenta[a]phenanthrene-17,2'(5H)-furan]-3,5'(2H)-dione). Its molecular formula is $C_{24}H_{30}O_3$. Drospirenone has the CAS registry number 67392-87-4 and the following structural formula:



Ethinyl estradiol is a synthetic estrogenic compound and has the chemical name of 19-nor-17α-pregna 1,3,5(10)-triene-20-yne-3,17-diol. Its molecular formula is $C_{20}H_{24}O_2$. Ethinyl estradiol has the CAS registry number 57-63-6 and the following structural formula:



Levomefolate calcium (AKA the calcium salt of L-5-methyltetrahydrofolate (L-5-methyl-THF) and the calcium salt of 5-methyl-(6S)-tetrahydrofolic acid) is a metabolite of vitamin B9 and has the chemical name of N-[4-[[(2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-(6S)-pteridinyl)methyl]amino]benzoyl]L-glutamic acid, calcium salt. Its molecular formula is $C_{20}H_{23}CaN_7O_6$. Levomefolate calcium has the CAS registry number 151533-22-1 and the following structural formula:



Levomefolate calcium is present in the approved product, BEYAZ™, as crystalline polymorph Form I.

(2) The approved product, BEYAZ™, was subject to regulatory review under the Federal Food, Drug and Cosmetic Act Section 505 (21 U.S.C. §355).

(3) The approved product, BEYAZ ™, received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355) on September 24, 2010 (NDA 022532).

(4) BEYAZ ™ contains drospirenone, ethinyl estradiol, and levomefolate calcium (polymorph Form I) as active ingredients.

Drospirenone and ethinyl estradiol, in combination, have been approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act since March 16, 2006 (Yaz ®; NDA 021676).

Levomefolate calcium has not been approved for commercial marketing or use under Section 505 or any other section of the Federal Food, Drug and Cosmetic Act prior to the approval of NDA 022532 by the Food and Drug Administration. It has also not been previously approved for commercial marketing or use under the Public Health Act or the Virus-Serum-Toxin Act.

In a telephone conversation on November 22, 2010 with Pamela Lucarelli, the FDA Regulatory Health Project Manager for NDA 022532, the undersigned was informed that FDA did not consider BEYAZ ™ to be either a new molecular entity (NME) or a new chemical entity (NCE). Ms. Lucarelli indicated that FDA considered BEYAZ ™ to be a Type 4/Type 7 entity. Type 4 means "new combination," and Type 7 means "Drug already

marketed, but without an approved NDA."

As set forth in 37 CFR 1.710(a), for a patent to be eligible for extension of the patent term the patent must claim a "product" as defined in 37 CFR 1.710(b), either alone or in combination with other ingredients that read on a composition that received permission for commercial marketing or use, or a method of using such a product, or a method of manufacturing such a product. The term "product" is defined in 37 CFR 1.710(b) as being, among other things, the active ingredient of a new human drug, as that term is used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.

Section 201, paragraph (p)(1) of the Federal Food, Drug, and Cosmetic Act, i.e., 21 U.S.C. 321(p)(1), defines "new drug" as:

> any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the condition prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act [enacted June 25, 1938] it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use.

Since levomefolate calcium (polymorph Form I) is an active ingredient of the new drug product BEYAZ ™, and regulatory review by the FDA was required before BEYAZ ™ could be marketed (see 35 U.S.C. §156(f)(2)(A) and 35 U.S.C. §156(a)(4)); and since this review permitted the first commercial marketing or use of the product under the provision of law under which such regulatory review period occurred, it is respectfully submitted that levomefolate calcium is a "product" as defined in 37 CFR 1.710(b), and a patent claiming such product is eligible for extension of patent term pursuant to 35 U.S.C. §156 and 37 CFR 1.710(a). See, for example, *Photocure ASA v. Kappos*, 603 F.3d 1372, 95 USPQ2d 1250 (Fed. Cir. 2010).

(5) This application for extension of patent term under 35 U.S.C. 156 is being submitted within the permitted 60 day period pursuant to 37 C.F.R. §1.720(f), which period is

believed to expire on November 23, 2010.

(6) The complete identification of the patent for which extension is being sought is as follows:

Inventors:	Rüdolf Muller, Rudolf Moser, and Thomas Egger
Patent Number:	6,441,168
Issue Date:	August 27, 2002
Expiration Date:	April 17, 2020

(7) See "Attachment A" for a complete copy of the patent identified in paragraph (6) hereof.

(8) A Certificate of Correction was issued with regard to U.S. Patent 6,441,168 on June 1, 2004 (the word "acids" in claim 15 was changed to 'acid"). A copy of the Certificate of Correction is included with the copy of the patent in Attachment A.

No Terminal Disclaimer or re-examination certificate have been issued with regard to U.S. Patent 6,441,168.

The maintenance fee for the 4th year was paid for U.S. Patent 6,441,168 on February 3, 2006, and the maintenance fee for the 8th year was paid for U.S. Patent 6,441,168 on January 29, 2010. Attached as "Attachment B" are copies of the Maintenance Fee Statement showing that the 4th year and 8th year maintenance fee payments has been made with respect to U.S. Patent 6,441,168.

(9) Claims of U.S. Patent 6,441,168 read on the approved product BEYAZ™ and a method of manufacturing an active ingredient of the approved product BEYAZ™. Specifically, the approved product BEYAZ ™ is covered under claims 1-4 and 8-14 of U.S. Patent 6,441,168, which claims cover levomefolate calcium (polymorph Form I), and a method of manufacturing same, which is an active ingredient in the approved product BEYAZ™. Claims 1-4 and 8-14 of U.S. Patent 6,441,168 are presented below, along with a demonstration of the manner in which these claims read on the approved product BEYAZ ™.

Claims:

1. A crystalline salt of 5-methyl-(6R,S)-, -(6S)- or -(6R)-tetrahydrofolic acid said crystalline salt having a water of crystallization of at least one equivalent per equivalent of 5-

methyltetrahydrofolic acid.

2. A crystalline salt according to claim 1, of 5-methyl-(6S)- or -(6R)-tetrahydrofolic acid.

3. A crystalline calcium salt according to claim 1, of 5-methyl-(6S)- and -(6R)-tetrahydrofolic acid having ≥ 3 equivalents of water.

4. A crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid with 2 theta values of 6.5, 13.3, 16.8 and 20.1 (Type I) said crystalline salt having a water of crystallization of at least one equivalent per equivalent of 5-methyltetrahydrofolic acid.

8. A method of producing crystalline salts of 5-methyl-(6R,S)-, -(6S)- and 5-methyl-(6R)-tetrahydrofolic acid, comprising subjecting a salt of 5-methyl-(6R,S)-, -(6S)- or -(6R)-tetrahydrofolic acid in a polar medium to a thermal treatment, at a temperature above 60° C, and thereafter crystallizing said salt from the resultant heated solution.

9. A method according to claim 8, wherein the crystallisation is effected after thermal treatment at a temperature above 85° C.

10. A method according to claim 8, wherein the crystallisation is effected from a solution.

11. A method according to claim 8, wherein the crystallisation is effected from a suspension.

12. A method according to claim 10, characterised in that crystallisation is effected from water or from a mixture of water and an organic solvent which is miscible with water.

13. A method according to claim 8, wherein said salt is an alkaline earth salt.

14. A method according to claim 8, wherein said salt is calcium.

Demonstration of the manner in which the claims read on the method of using the approved product:

BEYAZ™ is an combination oral contraceptive (COC) containing drospirenone, ethinyl estradiol, and levomefolate calcium (polymorph Form I) as the active ingredients. The dosing regimen of BEYAZ™ is packaged as blister packs each containing 28 film-coated tablets. An individual blister pack contains: 24 pink tablets each containing 3 mg drospirenone, 0.02 mg ethinyl estradiol as betadex clathrate, and 0.451 mg crystalline levomefolate calcium (polymorph Form I); and 4 light orange tablets each containing 0.451 mg crystalline levomefolate calcium (polymorph Form I).

Levomefolate calcium is also referred to as the calcium salt of 5-methyl-(6S)-tetrahydrofolic acid. As indicated in the patent, the crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid (Type I) typically contains at least three equivalents of water of crystallization per equivalent of 5-methyltetrahydrofolic acid. See column 2, lines 4-16. Thus, the crystalline levomefolate calcium (polymorph Form I) contained in the tablets of BEYAZ™ is a crystalline salt of 5-methyl-(6S)-tetrahydrofolic acid having a water of crystallization of at least one equivalent per equivalent of 5-methyltetrahydrofolic acid. Compare claims 1-4 of US 6,441,168.

Further, the patent discloses that crystalline levomefolate calcium (polymorph Form I) can be prepared by subjecting a salt of 5-methyl-(6S)-tetrahydrofolic acid in a polar medium to a thermal treatment at a temperature above 60° C, and thereafter crystallizing the salt. See, for example, column 2, lines 29-36 and 61-63. Compare claims 8-14.

(10) The relevant dates and information pursuant to 35 U.S.C. §156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(A) The Investigational New Drug Application (IND-72, 287) for BEYAZ™ was filed March 1, 2007 and became effective on April 4, 2007.

(B) The New Drug Application (NDA-22-532) for BEYAZ™ was initially submitted to the FDA on August 21, 2009, and received by the FDA on August 21, 2009.

(C) The New Drug Application (NDA-22-532) for BEYAZ™ was approved on September 24, 2010.

(11) A brief description of the significant activities undertaken by Applicant during the applicable regulatory review period is attached hereto as "Attachment C" and the dates applicable to such activities.

(12)(A) Applicant is of the opinion that U.S. Patent 6,441,168 is eligible for extension under 35 U.S.C. §156 because it satisfies all of the following requirements for such extension:

(a) 35 U.S.C. §156(a); 37 C.F.R. §1.720(a)

U.S. Patent 6,441,168 claims a product as defined in 37 C.F.R. §1.710(b)(1) and a method of manufacturing that product;

(b) 35 U.S.C. §156(a)(2); 37 C.F.R. §1.720(b)

The term of U.S. Patent 6,441,168 has never been previously extended;

(c) 35 U.S.C. §156(a)(3); 37 C.F.R. §1.730

This application for extension is submitted by the patent owner of record, in accordance with the requirement of 35 U.S.C. §156(d) and the rules of the U.S. Patent and Trademark Office, and signed by a registered practitioner on behalf of the patent owner;

(d) 35 U.S.C. §156(a)(4); 37 C.F.R. §1.720(d)

The product BEYAZ™ has been subject to a regulatory review period as defined in 35 U.S.C. §156(g) before its commercial marketing or use;

(e) 35 U.S.C. §156(a)(5)(A); 37 C.F.R. §1.720(e)(i)

The commercial marketing or use of the product BEYAZ™ after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug and Cosmetics Act (21 U.S.C. 360) under which such regulatory review period occurred;

(f) 35 U.S.C. §156(d)(1); 37 C.F.R. §1.720(f)

The application is submitted within the permitted 60 day period beginning on the date the product first received permission for commercial marketing or use;

(g) 35 U.S.C. §156(a)(1); 37 C.F.R. §1.720(g)

The term of U.S. Patent 6,441,168 has not expired before submission of this application;

(h) 35 U.S.C. §156(c)(4); 37 C.F.R. §1.720(h)

No other patent has been extended for the same regulatory review period for the product BEYAZ™.

(12)(B) Applicant is further of the opinion that the patent term U.S. Patent 6,441,168 for BEYAZ™ is eligible for an extension under 35 U.S.C. §156 of 834 days. The length of extension was determined pursuant to 37 C.F.R. §1.775 as follow:

(1) Determination of the length of the Regulatory Review Period

(i) The regulatory review period under 35 U.S.C. §156(g)(1)(B) began April 4, 2007 and ended September 24, 2010, which is a total of 1269 days which is the sum of (ii) and (iii) below;

(ii) The period of review under 35 U.S.C. §156(g)(1)(B)(i), the IND period, began on April 4, 2007 and ended on August 21, 2009, which is 870 days.

(iii) The period of review under 35 U.S.C. §156(g)(1)(B)(ii), the "Application Period," began on August 21, 2009 and ended May 6, 2010, which is 399 days.

(2) Determination of the length of the Regulatory Review Period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 12(B)(1)(i) (1269 days) less

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (August 27, 2002), which is zero (0) days, and

(ii) The number of days during which applicant did not act with due diligence, which is zero (0) days, and

(iii) One-half the number of days determined in subparagraph 12(B)(1)(ii) after subtracting there from the number of days of subparagraphs (12)(B)(2)(i) and (12)(B)(2)(ii) or 435 days (i.e., ½(870-0-0) wherein half days are ignored for purpose of subtraction),

which totals 834 days (i.e., 1269-0-0-½(870-0-0).

(3) The number of days as determined in subparagraph 12(B)(2) (834 days) when added to the original term of the patent would result in the date July 30, 2022.

(4) Fourteen (14 years) when added to the date of the NDA approval (September

24, 2010) would result in the date September 24, 2024.

(5) The earliest date as determined in paragraphs 12(B)(3) and 12(B)(4) is July 30, 2022.

(6) The issuance of the original exemption occurred after September 24, 1984. Five (5) years when added to the original expiration date of the patent (April 17, 2020) would result in the date April 17, 2025.

(7) The earlier date as determined in paragraphs 12(B)(5) and 12(B)(6) is July 30, 2022.

Therefore, the length of extension of patent term claimed by applicant is 834 days or two (2) years and 104 days.

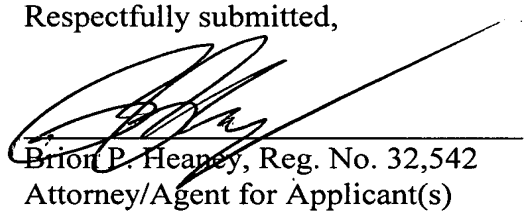
(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any Information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee of $1,120 pursuant to 37 C.F.R. §1.20(j) for receiving and acting upon this application is to be charged to the counsel's Deposit Account 13-3402.

(15) All inquiries and correspondence relating to this application are to be directed to the undersigned.

Pursuant to 37 C.F.R. §1.740(b), two copies of these application papers, certified as such, are being submitted herewith.

Respectfully submitted,



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Date: November 23, 2010

ATTACHMENT A

1. **Complete copy of US Patent No. 6,441,138, including Certificate of Correction of June 1, 2004**

ATTACHMENT B

1. **Maintenance Fee Statement for payment of 4th year annuity for US Patent No. 6,441,168 on February 3, 2006**

2. **Maintenance Fee Statement for payment of 8th year annuity for US Patent No. 6,441,168 on January 29, 2010**

ATTACHMENT C

1. **IND 72,287 Chron Log (06/06/05 to 06/03/10)**

2. **NDA 22-532 (NATAZIA) Chron Log (08/21/09 to 09/24/10)**

3. **FDA Approval Letter dated September 24, 2010 (acknowledgement of receipt of submissions in second paragraph)**

US006441168B1

(12) **United States Patent**
Müller et al.

(10) **Patent No.: US 6,441,168 B1**
(45) **Date of Patent: Aug. 27, 2002**

(54) **STABLE CRYSTALLINE SALTS OF 5-METHYLTETRAHYDROFOLIC ACID**

(75) Inventors: **Rudolf Müller**; **Rudolf Moser**, both of Schaffhausen; **Thomas Egger**, Effretikon, all of (CH)

(73) Assignee: **Eprova AG**, Schaffhausen (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/551,405**

(22) Filed: **Apr. 17, 2000**

(30) **Foreign Application Priority Data**

Apr. 15, 1999 (CH) 695/99

(51) **Int. Cl.**[7] **C07D 475/04**
(52) **U.S. Cl.** **544/258**
(58) **Field of Search** 544/258

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Derwent English abstract of EP 539 987.

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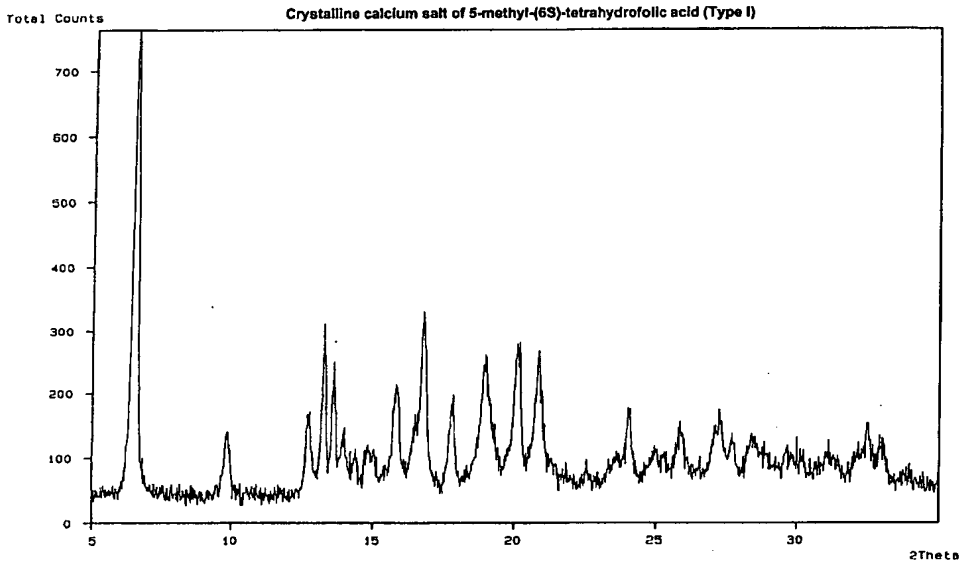
Primary Examiner—Richard L. Raymond
Assistant Examiner—Thomas C McKenzie
(74) *Attorney, Agent, or Firm*—Millen, White, Zelano & Branigan, P.C.

(57) **ABSTRACT**

This invention relates to stable crystalline salts of 5-methyl-(6R,S)-, -(6S)- and -(6R)-tetrahydrofolic acid, to methods of producing these salts and to the use thereof use as a constituent for the production of drugs or as a food additive, and to preparations containing these salts.

17 Claims, 5 Drawing Sheets



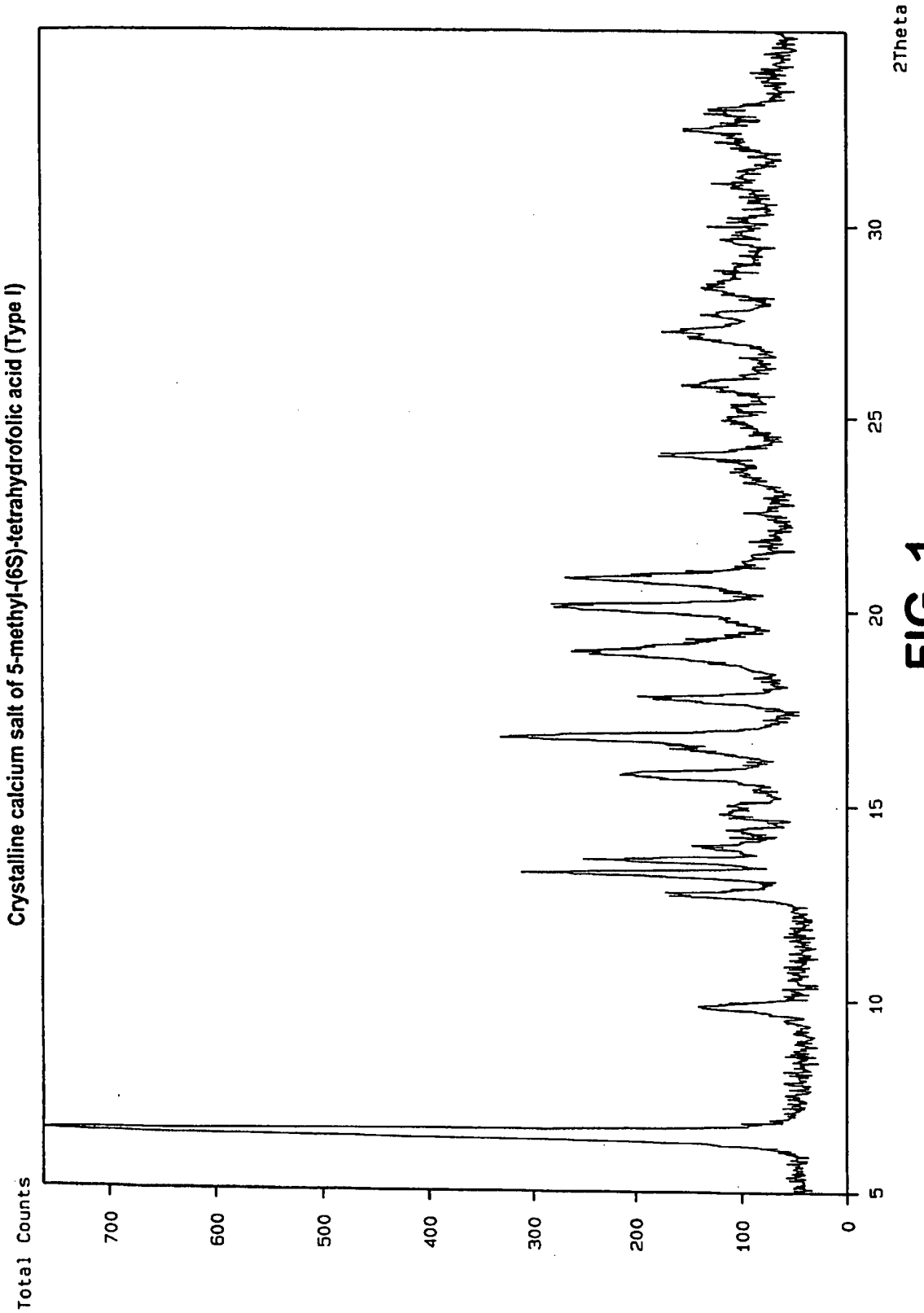

Crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid (Type I)
Total Counts
700
600
500
400
300
200
100
0
5
10
15
20
25
30
2Theta

FIG. 1

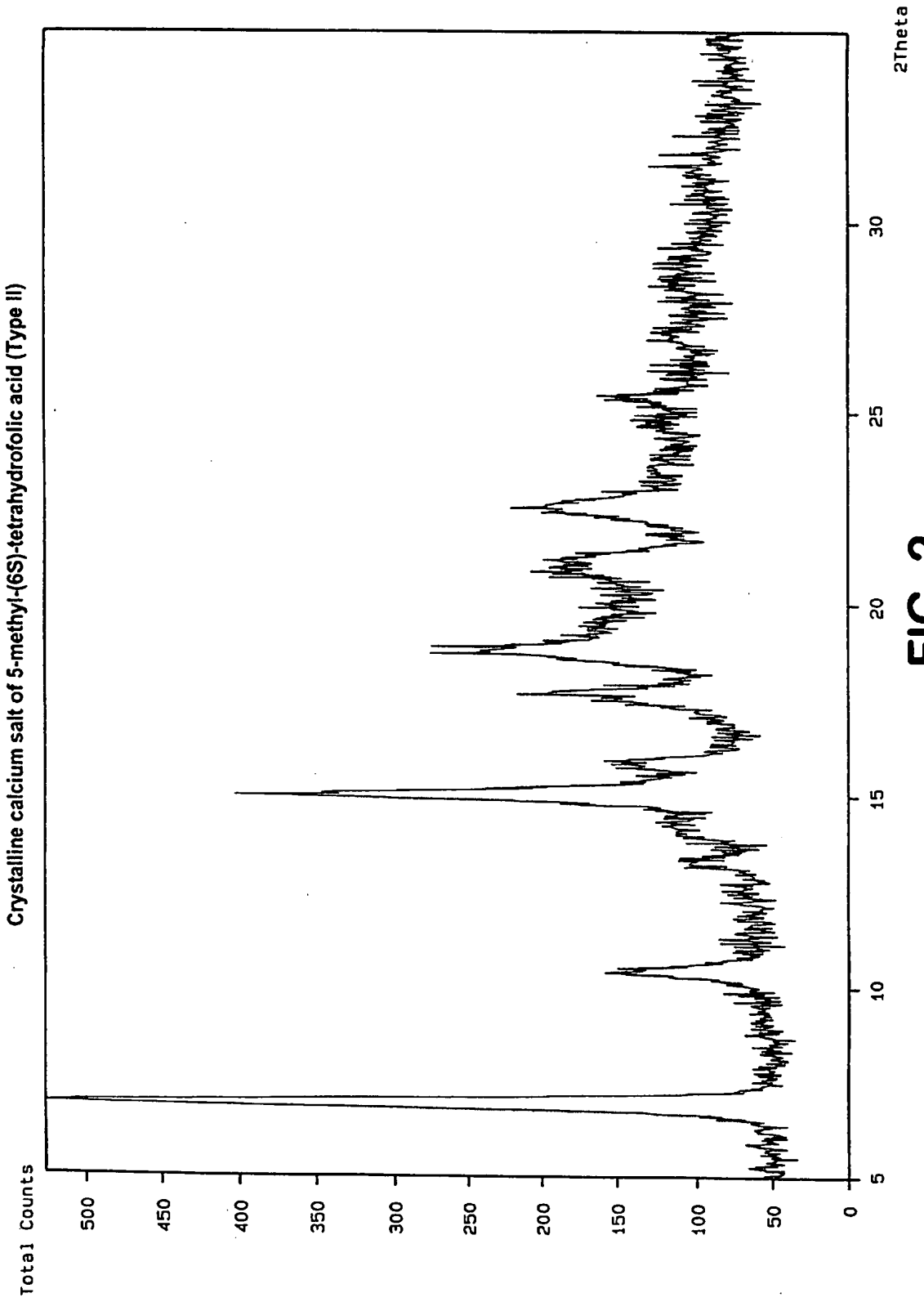

Crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid (Type II)
Total Counts
500
450
400
350
300
250
200
150
100
50
0
5
10
15
20
25
30
2Theta

FIG. 2

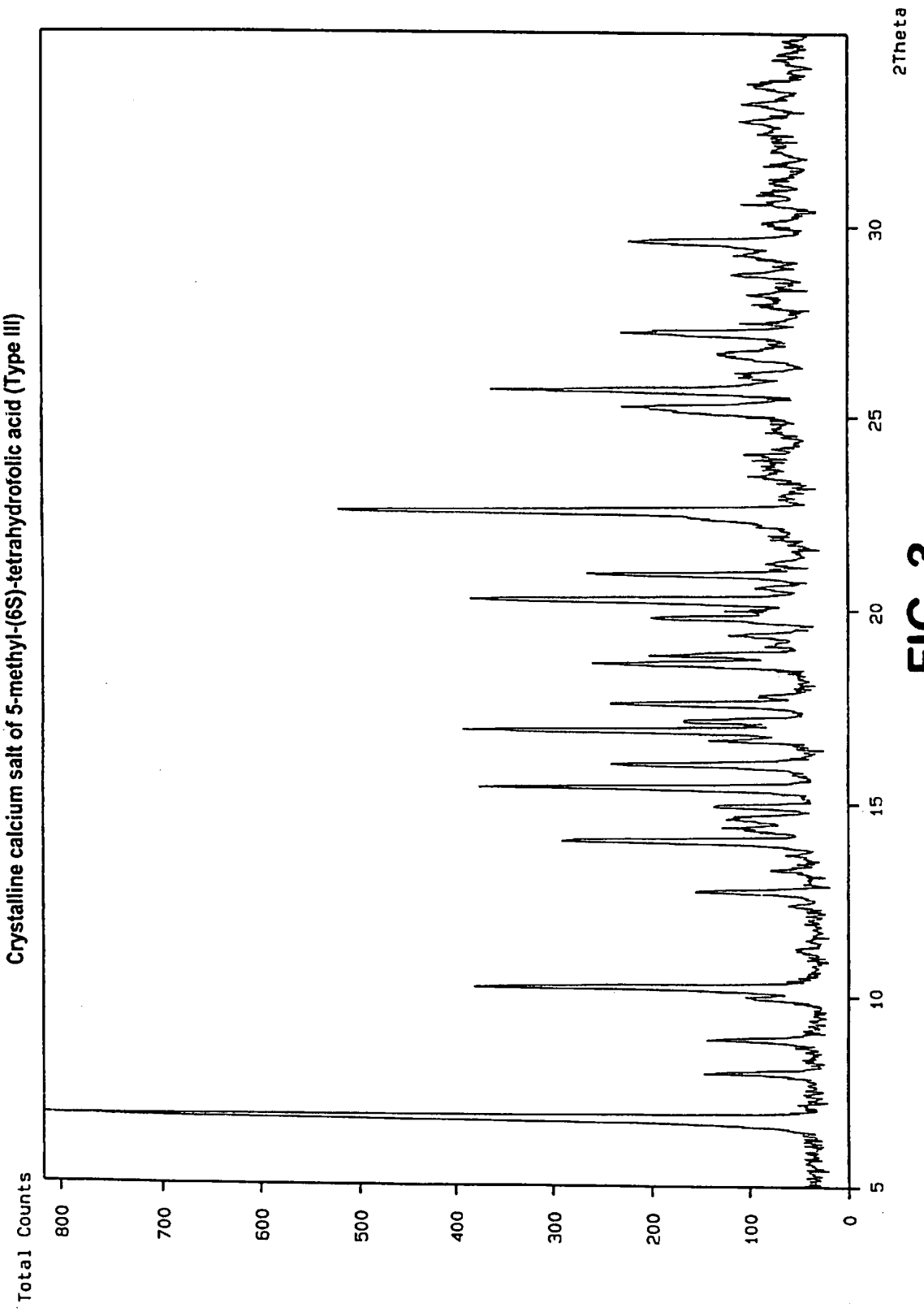

Crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid (Type III)
Total Counts
800
700
600
500
400
300
200
100
0
5
10
15
20
25
30
2Theta

FIG. 3

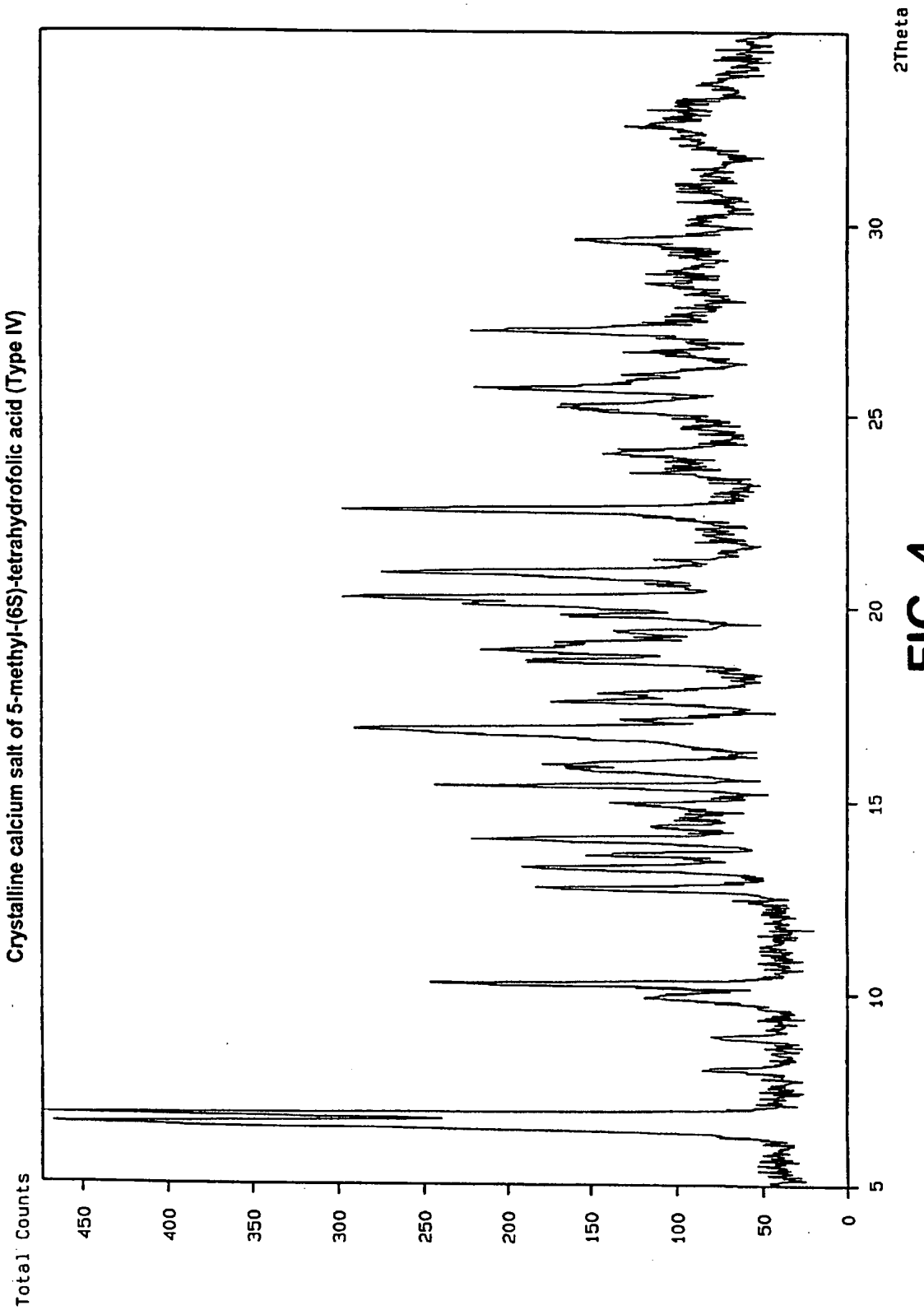

Crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid (Type IV)
Total Counts
2Theta
0
50
100
150
200
250
300
350
400
450
5
10
15
20
25
30

FIG. 4

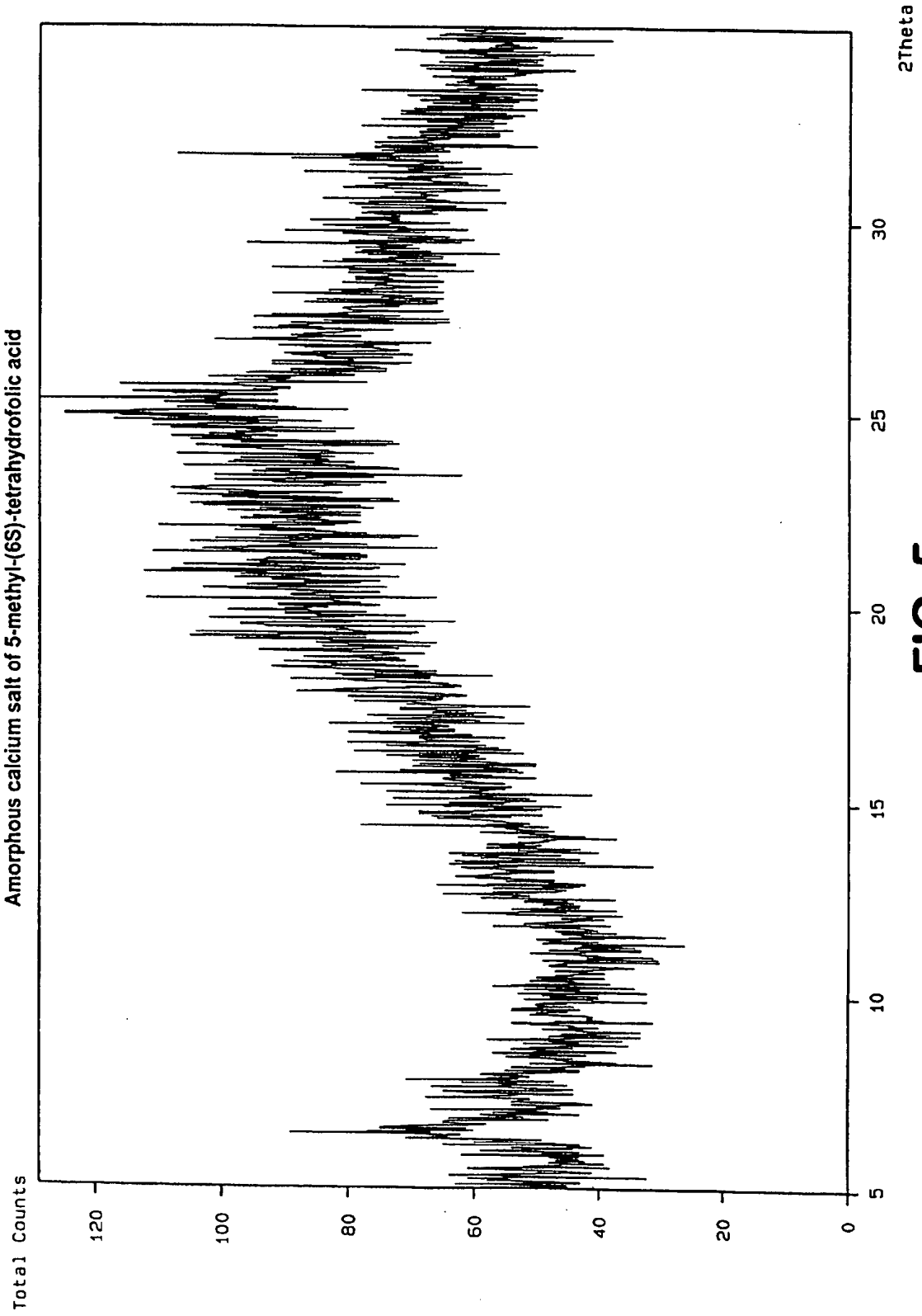

Amorphous calcium salt of 5-methyl-(6S)-tetrahydrofolic acid
Total Counts
120
100
80
60
40
20
0
5
10
15
20
25
30
2Theta

FIG. 5

STABLE CRYSTALLINE SALTS OF 5-METHYLTETRAHYDROFOLIC ACID

FIELD OF THE INVENTION

This invention relates to crystalline salts of N-[4-[[(2-amino-1,4,5,6,7,8hexahydro-4-oxo-5-methyl-(6S)-, -(6R)- and -(6R,S)-pteridinyl)methyl]amino]benzoyl-L-glutamic acid (hereinafter called salts of 5-methyltetrahydrofolic acid), to the use thereof, and to a method of producing them.

BACKGROUND OF THE INVENTION

Tetrahydrofolates are predominantly used as 5-formyltetrahydrofolic acid and the salts thereof (leucovorin) or as 5-methyltetrahydrofolic acid and the salts thereof, for the treatment of megaloblastic folic acid anaemia, as an antidote for increasing the compatibility of folic acid antagonists, particularly of aminopterin and methotrexate in cancer therapy ("antifolate rescue"), for increasing the therapeutic effect of fluorinated pyrimidines and for the treatment of autoimmune diseases such as psoriasis and rheumatoid arthritis, for increasing the compatibility of certain antiparasitic formulations, for instance trimethoprim-sulfamethoxazole, and for reducing the toxicity of dideazatetrahydrofolates in chemotherapy. 5-methyltetrahydrofolic acid is used in particular as a drug and as a food additive, as a vitamin preparation, for the prevention of neural tube defects, for the treatment of depressive illnesses, and for influencing the homocysteine level.

5-methyltetrahydrofolic acid and salts thereof are extremely unstable, and in particular are highly susceptible to oxidation [see also A. L. Fitzhugh, Pteridines 4 (4), 187–191 (1993) in this respect] and are therefore difficult to produce at a level of purity which is acceptable for a pharmaceutical active ingredient or a food additive.

Various methods, such as excluding oxygen as completely as possible or the addition of antioxidants such as ascorbic acid or reduced L-glutathione, have been employed in order to overcome the instability of 5-methyltetrahydrofolic acid. However, it is scarcely possible completely to exclude oxygen during use, and even then this is only possible at very considerable cost, and the addition of antioxidants is likewise not always possible. Accordingly, it has not been possible hitherto to identify a commercially feasible method which is suitable for the production of salts of 5-methyltetrahydrofolic acid which are satisfactorily stable and which are of high purity.

SUMMARY OF THE INVENTION

Surprisingly, it has now been found that salts of 5-methyltetrahydrofolic acid which exhibit high chemical purity and excellent stability can be obtained by crystallising the corresponding salt from a polar medium after subjecting the solution to thermal treatment at a temperature above 60° C. The highly crystalline salts of 5-methyl-tetrahydrofolic acid which are thus obtained are stable at room temperature, practically without-limitation They are suitable as a constituent or as a starting material for the production of drug forms or food additives.

Accordingly, the present invention relates to crystalline salts of 5-methyltetrahydrofolic acid. Alkaline earth salts, particularly the calcium salt, are preferably used as the salts of 5-methyltetrahydrofolic acid for crystallisation. These crystalline salts of 5-methyltetrahydrofolic acid exhibit a purity, which has never been achieved hitherto, of >98%,

together with a stability, with respect to the initial value thereof and which has never been achieved hitherto, of >98% after storage for 6 months in air at 25° C. and 60% relative atmospheric humidity. The crystalline calcium salts of 5-methyl-(6S)-tetrahydrofolic acid exist in four different crystalline modifications (Type I, Type II, Type III and Type IV) and exhibit sharp bands when subjected to X-ray powder diffraction measurements (see Table 1 to Table 4 in this respect). Selected 2 theta values for the different crystalline modifications are 6.5, 13.3, 16.8 and 20.1 (Type I); 5.3, 6.9, 18.7 and 21.1 (Type II); 6.8, 10.2, 15.4 and 22.5 (Type III); and 6.6, 15.9, 20.2 and 22.5 (Type IV). Crystalline calcium salts of 5-methyltetrahydrofolic acid have a content of water of crystallisation of at least 1 equivalent of water per 1 equivalent of 5-methyltetrahydrofolic acid. Thus the Type I modification typically contains $\geqq 3$ equivalents of water, the Type II modification typically contains $\leqq 2$ equivalents water and the Type III and Type IV modifications typically contain $\leqq 5$ equivalents of water.

Other Salts of 5-methyl-(6R)-tetrahydrofolic acid and salts of 5-methyl-(6R,S)-tetrahydrofolic acid can likewise be obtained in highly crystalline form.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. **1–4** are self-explanatory X-ray powder diffraction diagrams of the 4 crystalline modifications of the calcium salts of the invention, and FIG. **5** is a diagram of the amorphous salt.

The present invention further relates to a method of producing highly crystalline salts of 5-methyltetrahydrofolic acid, which is characterised in that the corresponding salt of 5-methyltetrahydrofolic acid is crystallised. In this method, crystallisation of salts of 5-methyltetrahydrofolic acid is effected from a polar medium after thermal treatment at a temperature above 60° C., particularly above 85° C.

Substances which are particularly suitable as the polar medium include water or a mixture of water and an organic solvent which is miscible with water, such as watersoluble alcohols, e.g. methanol, ethanol, n-propanol, iso-propanol or ethylene glycol, a low molecular weight aliphatic water-soluble carboxylic acid e.g. formic acid, acetic acid or lactic acid, or water-soluble amides e.g. formamide, dimethylformamide, dimethylacetamide, 1-methylpyrrolidone, 2-methylpyrrolidone or 2-piperidinone. There are no particular restrictions with regard to the type of solvent used and with regard to the mixture ratio, since crystalline salts of 5-methyltetrahydrofolic acid generally exhibit solubilities which are lower than those of the corresponding amorphous forms.

Crystallisation is preferably effected from solutions. It is also possible to effect crystallisation from a suspension, however.

Aside from calcium salts, still further salts of 5-methyl-(6R,S) or (6R) or (6S) hydrofolic acids include but are not limited to other alkaline earth salts, for example, magnesium can be obtained in highly crystalline forms.

The different crystalline modifications can be converted into one another by further thermal treatments at temperatures above 60° C. Thus Type I, which is produced by crystallisation from a polar medium after thermal treatment at a temperature above 60° C., can be converted into Type II by drying sufficiently, e.g. under vacuum at 70° C., can be converted into Type III by sufficient thermal treatment at a temperature above 90° C., and can be converted into Type IV by sufficient thermal treatment at a temperature above 95° C.

Type II can be converted into Type 1 again by adding water to the crystals, e.g. by treatment with water in a humidity cabinet at 90° C.

Crystallisation of the salts of 5-methyltetrahydrofolic acid occurs spontaneously or is effected by seeding with the corresponding crystalline salt of 5-methyltetrahydrofolic acid.

A suitable, preferred starting material for crystallisation is pure, amorphous or crystalline 5-methyl(6S)- or -(6R)-tetrahydrofolic acid. Racemic 5-methyl-(6R,S) tetrahydrofolic acid can also be used, however, as can enriched 5-methyl-(6S)-, -(6R)- or -(6R,S)-tetrahydrofolic acid.

By using amorphous or partly crystalline, optically pure 5-methyltetrahydrofolic acid or salts thereof as the starting material for crystallisation, essentially crystalline salts of 5-methyltetrahydrofolic acid of a purity which has never been achieved hitherto, together with a stability which has never been achieved hitherto, are obtained by the method described here.

The present invention also relates to the use of highly crystalline salts of 5-methyltetrahydrofolic acid as a constituent for the production of drugs or food additive substances or for the production of other tetrahydrofolic acid derivatives, since, on account of their excellent stability in solid form, crystalline salts of 5-methyltetrahydrofolic acid are of a very good quality which remains constant with time, practically without limits. The present invention also relates to preparations containing highly crystalline salts of 5-methyltetrahydrofolic acid. These preparations are produced by known methods. They are employed analogously to the use of known substances from the field of tetrahydrofolates, such as 5-formyltetrahydrofolic acid (leucovorin) for example.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight.

EXAMPLES WHICH ILLUSTRATE THE INVENTION

The content of 5-methyltetrahydrofolic acid salt which is quoted in the examples was s determined by HPLC in each case and is given as % area. The water content was determined by a Karl Fischer method.

Example 1

Stabilities

In order to determine the stabilities of the crystalline salts of 5-methyltetrahydrofolic acid, the substances were stored, together with comparison specimens, in air at 25° C. and at 60% relative humidity. The content of 5-methyltetrahydrofolic acid salt remaining was measured at periodic intervals and is given by comparison with the initial value.

	Time of storage in months					
	0	3	6	12	18	88
Crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid	100%	98.6%	98.7%	99.1%	99.0%	97.8%
Amorphous calcium salt of 5-methyl-(6S)-tetrahydrofolic acid	100%			84.2%		

The crystalline salts of 5-methyltetrahydrofolic acid were still very light in colour even after an extended period of storage. In contrast thereto, the amorphous samples exhibited considerable discoloration, which occurred very rapidly.

Example 2

X-ray Powder Plots

X-ray powder plots (diffraction spectra) of these substances were recorded in order to characterise the structural properties (crystalline modifications) of the crystalline salts of 5-methyltetrahydrofolic acid.

The crystalline salts of 5-methyltetrahydrofolic acid exhibited spectra of good resolution, with sharp bands and low background effects. The spectra indicated highly crystalline constituents.

Examples of spectra are illustrated in FIG. **1** (Type I), FIG. **2** (Type II), FIG. **3** (Type III) and FIG. **4** (Type IV), and are presented in Table 1 (Type I), Table 2 (Type II), Table 3 (Type III) and Table 4 (Type IV). For comparison, a spectrum of an amorphous sample was also recorded under analogous conditions and is presented as FIG. **5** (amorphous).

Selected 2 theta values for the different crystalline modifications of the crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid are listed below:

Type	Selected 2 theta values
Type I	6.5, 13.3, 16.8 and 20.1
Type II	5.3, 6.9, 18.7 and 21.1
Type III	6.8, 10.2, 15.4 and 22.5
Type IV	6.6, 15.9, 20.2 and 22.5

Example 3

Solubilities

The solubility of the crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid is given in the following Table:

	Solubility at 20° C. in	
Type	0.9% NaCl	water
Type I	1.6%	1.1%
Type II	5.8%	3.8%
Type III	1.5%	1.0%

Example 4

Amorphous Calcium Salt of 5-Methyl-(6S)-tetrahydrofolic Acid

7.5 g 5-methyl-(6S)-tetrahydrofolic acid were introduced into 75 ml water at room temperature whilst passing N_2 into

the batch, and the batch was adjusted to pH 12 with aqueous 30% sodium hydroxide solution. The clear solution which was thus obtained was adjusted to pH 7.5 with 37% hydrochloric acid and was treated with a solution of 7.15 g calcium chloride $6H_2O$ in 11.7 ml water. The white suspension which was formed was stirred for 5 hours and was then filtered under suction at room temperature. The solid was washed with water and was dried under vacuum at 45° C.

5.8 g of a white, amorphous calcium salt of 5-methyl-(6S)-tetrahydrofolic acid were obtained, which had a content of 98.0% and a 6S fraction corresponding to 99.6%.

Even after treating this substance at 60° C. in a humidity cabinet, no crystalline fractions could be determined either under a polarising microscope or by X-ray diffraction measurements.

Example 5

Crystalline Calcium Salt of 5-Methyl-(6 R,S)-tetrahydrofolic Acid

70 g 5-methyl-(6R, S)-tetrahydrofolic acid were placed in a vessel in 780 ml water and the batch was adjusted to pH 7.5 with 45.2 g of 30% NaOH. The clear, slightly reddish solution was treated with a solution of 62.7 g calcium chloride $6H_2O$ in 140 ml water, and the solid was filtered off and washed with a little water. The crude product which was thus obtained was suspended in water and treated at 90° C. for 24 hours.

74.0 g of a white, crystalline calcium salt of 5-methyl-(6R,S)-tetrahydrofolic acid was obtained, with a content of 99.1%.

Example 6

Crystalline Calcium Salt of 5-Methyl-(6R)-tetrahydrofolic Acid

16.5 g 5-methyl-(6R)-tetrahydrofolic acid were placed in a vessel in 100 ml water at 92° C. with 50 g calcium chloride $6H_2O$. The clear, slightly yellowish suspension was stirred for 10 minutes at 91° C., and the solid was filtered off, washed with a little water and dried at 35° C. under vacuum.

15.4 g of a light beige crystalline calcium salt of 5-methyl-(6R)-tetrahydrofolic acid were obtained, with a content of 97.9% and a water content of 7.8%.

Example 7

Type I

130 kg water were placed in a vessel and 12.8 kg 5-methyl-(6S)-tetrahydrofolic acid were introduced. The pH was adjusted to 11.6 with about 9.1 kg of 30% NaOH, and was then adjusted to 7.6 with about 1.9 kg of 37% hydrochloric acid. A suspension containing 0.3 kg carbon and 0.3 kg Cellflock was added to the clear solution. The solid was filtered off and washed with 13 litres of water. The filtrate was treated with a solution containing 8.3 kg calcium chloride $2H_2O$, heated to 90° C. and stirred for 30 minutes. The product was filtered hot and was washed with 2×20 kg water. The moist crude product which was thus obtained was slurried in 115 litres of water, heated to 90° C., immediately filtered hot, washed with 2×20 kg water, and dried at 40° C. under vacuum.

11.6 kg of a white, crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid (Type I) were obtained, which had a purity of 99.0% and a water content of 14.5%.

Example 8

Type I

1600 ml water were placed in a vessel and 194 g 5-methyl-(6S)-tetrahydrofolic acid were introduced. The pH was adjusted to 7.0 with about 80 ml of 30% NaOH. A suspension containing 20 g carbon and 20 g Cellflock in 190 ml water was added to the clear solution. The solid was filtered off and washed with water. The filtrate was treated with 950 ml of a 5.5 M calcium chloride solution, heated to 90° C. and stirred for 60 minutes. The product was filtered hot, washed with water, and dried at 45° C. under vacuum.

156.2 g of a white, crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid (Type I) were obtained, with a purity of 99.7% and a 6S fraction of 99.9%.

Example 9

Type 1 and Conversion Into Type II

554 g water were placed in a vessel and 53.1 g 5-methyl-(6S)-tetrahydrofolic acid were introduced. The pH was adjusted to 7.5 with 30% NaOH. 1.3 g carbon, 1.3 g Cellflock and 19.5 g water were added to the clear solution. The suspension was filtered and the solid was washed with 55 ml water. The filtrate was treated with a solution of 52.0 g calcium chloride $6H_2O$ in 84.6 g water, and was heated to 90° C. and seeded with 100 mg of the crystalline calcium salt of 5-methyltetrahydrofolic acid. After crystallisation had occurred, the product was filtered hot at 90° C. and was washed with 2×103 g water. The moist crude product which was thus obtained was slurried in 480 ml water, heated to 90° C., immediately filtered hot, washed as above, and dried at 45° C. under vacuum.

47.5 g of a white, crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid (Type I) were obtained, with a purity of 98.8% and a water content of 12.2%.

This Type I modification could be converted into the Type II modification with a water content of 5.0% by drying it at 70° C. under vacuum for 30 minutes.

Example 10

Type III

15.8 9 of the calcium salt of 5-methyl-(6S)-tetrahydrofolic acid were heated to 95° C. in 140 ml water whilst passing N_2 through the batch. After 30 minutes at 95° C. the white suspension was filtered hot under suction, and the solid was washed with water and dried at 35° C. under vacuum.

14.0 g of a white, crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid (Type III) was obtained, with a content of 98.9% and a 6S fraction of 99.9%.

Example 11

Type IV

20.0 g of the calcium salt of 5-methyl-(6S)-tetrahydrofolic acid were heated to 100° C. in 180 ml water whilst passing N_2 through the batch. After 30 minutes at 100° C. the white suspension was filtered hot under suction, and the solid was washed with water and dried at 25° C. under vacuum.

16.9 g of a white, crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid (Type IV) were obtained, with a content of 98.3% and a water content of 9.9%.

By drying it at 65° C. under vacuum, the water content of this product could be reduced to 5.5% without a different crystalline modification being obtained in the course of this procedure.

Examples of Uses of the Crystalline Material

(a) As constituent for the production of drugs:

Beside the well known uses of 5-formyltetrahydrofolic acid previously described, reference is invited to U.S. Ser. No. 09/095,572 for pharmaceutical preparations including pharmaceutically acceptable excipients, as well as dosage ranges of 5-methyltetrahydrofolic acid.

(b) As food additive:

The range of possible applications as food additive is very wide (from single preparations to multivitamin preparations and grain to breakfast foods). Please refer to e.g. WO 97/27764, SAMSF/Bailey et al., for examples (e.g. examples 1, 2, 6, 8 and 9 all contain formulas with 5-methyltetrahydrofolic acid).

(c) For the production of other tetrahydrofolic acid derivatives:

Under "other tetrahydrofolic acid derivatives", other salts of 5-methyltetrahydrofolic acid and the free acid itself are especially included.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples. Also, the preceding specific embodiments are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The entire disclosure of all applications, patents and publications, cited above and below, and of corresponding Swiss application 695/99, are hereby incorporated by reference.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

TABLE 1

Crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid (Type I)

Diffractometer : Transmission
Monochromator : Curved Ge (111)
Wavelength : 1.540598 Cu
Detector : Linear PSD
Scan Mode : Debye-Scherrer/Moving PSD/Fixed omega
2Theta scan
! Peak search parameters : Expected halfwidth : .150
! Significance level : 2.5
! Peak height level : 10
Peaklist [Range 1 : 2Theta = 5.000 34.980 .020 Imax = 765]

! D	2Theta	I (rel)	I (abs)	FWHM	h	k	l
13.474630	6.5544	100.0	755	.2200			
8.979750	9.8420	18.5	140	.1600			
6.936035	12.7526	20.3	153	.1600			
6.662427	13.2786	38.3	289	.0800			
6.497896	13.6164	29.4	222	.1200			
6.323596	13.9935	18.8	142	.0200			
6.148863	14.3933	14.0	106	.0400			
5.966675	14.8352	15.5	117	.1200			
5.593548	15.8309	27.5	208	.2200			
5.368022	16.5006	19.7	149	.1127			
5.282104	16.7709	42.5	321	.2000			
4.977751	17.8044	23.6	178	.1800			
4.672452	18.9782	32.7	247	.2800			
4.411916	20.1102	34.8	263	.0800			

TABLE 1-continued

Crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid (Type I)

Diffractometer : Transmission
Monochromator : Curved Ge (111)
Wavelength : 1.540598 Cu
Detector : Linear PSD
Scan Mode : Debye-Scherrer/Moving PSD/Fixed omega
2Theta scan
! Peak search parameters : Expected halfwidth : .150
! Significance level : 2.5
! Peak height level : 10
Peaklist [Range 1 : 2Theta = 5.000 34.980 .020 Imax = 765]

! D	2Theta	I (rel)	I (abs)	FWHM	h	k	l
4.257688	20.8467	34.2	258	.2600			
3.761157	23.6360	13.3	100	.0400			
3.699455	24.0361	22.3	168	.1400			
3.558431	25.0037	14.8	112	.1000			
3.439070	25.8864	21.0	159	.1400			
3.272550	27.2283	22.1	167	.2800			
3.218939	27.6907	17.0	129	.1400			
3.140884	28.3931	17.2	130	.0800			
3.013536	29.6198	13.9	105	.1000			
2.873482	31.0991	15.1	114	.0200			
2.782802	32.1395	16.6	125	.0200			
2.754830	32.4748	20.2	152	.0600			
2.713309	32.9858	15.4	116	.1127			

TABLE 2

Crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid (Type II)

Diffractometer : Transmission
Monochromator : Curved Ge (111)
Wavelength : 1.540598 Cu
Detector : Linear PSD
Scan Mode : Debye-Scherrer/Moving PSD/Fixed omega
2Theta scan
! Peak search parameters : Expected halfwidth : .150
! Significance level : 2.5
! Peak height level : 10
Peaklist [Range 1 : 2Theta = 5.000 34.980 .020 Imax = 526]

! D	2Theta	I (rel)	I (abs)	FWHM	h	k	l
12.720530	6.9434	100.0	517	.2600			
8.508053	10.3891	29.4	152	.2400			
6.631466	13.3409	19.6	101	.1200			
5.883504	15.0461	71.2	368	.2200			
5.580025	15.8696	27.8	144	.0800			
5.010988	17.6854	42.5	220	.1400			
4.730443	18.7434	53.6	277	.1400			
4.215807	21.0561	35.5	184	.0400			
3.943879	22.5263	38.8	201	.3600			
3.581969	24.8368	24.8	128	.0200			
3.493985	25.4726	29.6	153	.0400			
3.309171	26.9212	22.7	117	.0200			

TABLE 3

Crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid (Type III)

Diffractometer : Transmission
Monochromator : Curved Ge (111)
Wavelength : 1.540598 Cu
Detector : Linear PSD
Scan Mode : Debye-Scherrer/Moving PSD/Fixed omega
2Theta scan
! Peak search parameters : Expected halfwidth : .150
! Significance level : 2.5
! Peak height level : 10
Peaklist [Range 1 : 2Theta = 5.000 34.980 .020 Imax = 817]

!	D	2Theta	I (rel)	I (abs)	FWHM	h	k	l
	12.933490	6.8289	100.0	786	.1200			
	11.036740	8.0043	18.9	149	.0400			
	9.945525	8.8842	18.4	145	.1000			
	8.877709	9.9554	12.4	98	.0796			
	8.640580	10.2293	49.6	390	.1000			
	7.873330	11.2292	6.4	50	.1000			
	7.144004	12.3799	7.6	59	.0800			
	6.948557	12.7295	20.3	159	.1000			
	6.659956	13.2835	10.1	80	.0400			
	6.466239	13.6834	7.6	60	.0200			
	6.305060	14.0349	37.6	296	.1000			
	6.154434	14.3802	16.4	129	.0400			
	6.057193	14.6123	15.3	121	.0600			
	5.920458	14.9517	17.6	139	.1000			
	5.738533	15.4285	48.9	385	.1000			
	5.530167	16.0136	30.3	238	.1000			
	5.322477	16.6428	18.1	143	.0600			
	5.245302	16.8894	47.4	372	.0800			
	5.154604	17.1888	20.9	164	.0796			
	5.038273	17.5888	30.8	242	.1000			
	4.980502	17.7945	10.7	84	.0796			
	4.759336	18.6286	31.6	248	.1200			
	4.702846	18.8544	24.3	191	.0796			
	4.575841	19.3827	15.6	122	.0800			
	4.478961	19.8061	25.9	204	.1000			
	4.377158	20.2716	48.1	378	.1000			
	4.309006	20.5957	11.9	93	.0796			
	4.242777	20.9207	31.3	246	.0800			
	4.051441	21.9207	10.3	81	.0200			
	3.940356	22.5467	67.8	533	.1200			
	3.782452	23.5010	12.4	98	.0400			
	3.609291	24.6458	9.5	75	.0200			
	3.523157	25.2582	27.0	212	.2000			
	3.460874	25.7205	43.4	341	.0800			
	3.408545	26.1223	12.4	98	.0796			
	3.341048	26.6596	16.1	127	.2000			
	3.273575	27.2196	28.4	223	.1400			
	3.188038	27.9645	12.6	99	.0200			
	3.160110	28.2168	12.5	98	.0400			
	3.103472	28.7427	15.0	118	.0800			
	3.052658	29.2317	13.9	109	.0600			
	3.017419	29.5808	27.7	218	.1400			
	2.970195	30.0621	10.6	83	.1200			
	2.921067	30.5800	13.9	109	.0200			
	2.899222	30.8161	9.6	76	.0796			
	2.870572	31.1314	9.6	75	.0400			
	2.830661	31.5817	11.0	86	.0200			
	2.758126	32.4349	11.3	89	.0400			
	2.733265	32.7382	13.2	104	.0600			
	2.695836	33.2058	13.7	108	.0800			
	2.660160	33.6643	11.7	92	.1000			
	2.609572	34.3369	9.2	72	.0200			

TABLE 4

Crystalline calcium salt of
5-methyl-(6S)-tetrahydrofolic acid (Type IV)

Diffractometer : Transmission
Monochromator : Curved Ge (111)
Wavelength : 1.540598 Cu
Detector : Linear PSD
Scan Mode : Debye-Scherrer/Moving PSD/Fixed omega
2Theta scan
! Peak search parameters : Expected halfwidth : .150
! Significance level : 2.5
! Peak height level : 10
Peaklist [Range 1 : 2Theta = 5.000 34.980 .020 Imax = 473]

!	D	2Theta	I (rel)	I (abs)	FWHM	h	k	l
	13.398610	6.5916	97.7	446	.1600			
	12.930100	6.8307	100.0	457	.0915			
	11.033220	8.0069	19.2	88	.0800			
	9.952926	8.8776	16.7	76	.1200			
	8.912272	9.9167	25.5	116	.1600			

TABLE 4-continued

Crystalline calcium salt of
5-methyl-(6S)-tetrahydrofolic acid (Type IV)

Diffractometer : Transmission
Monochromator : Curved Ge (111)
Wavelength : 1.540598 Cu
Detector : Linear PSD
Scan Mode : Debye-Scherrer/Moving PSD/Fixed omega
2Theta scan
! Peak search parameters : Expected halfwidth : .150
! Significance level : 2.5
! Peak height level : 10
Peaklist [Range 1 : 2Theta = 5.000 34.980 .020 Imax = 473]

!	D	2Theta	I (rel)	I (abs)	FWHM	h	k	l
	8.626970	10.2455	48.9	223	.0800			
	6.931997	12.7600	37.4	171	.1000			
	6.651761	13.3000	39.7	181	.1200			
	6.499623	13.6127	32.8	150	.0800			
	6.309299	14.0254	47.0	215	.1600			
	6.161306	14.3641	25.1	115	.1200			
	5.917463	14.9593	27.0	124	.1000			
	5.736254	15.4347	49.8	227	.0800			
	5.544314	15.9724	36.7	168	.1600			
	5.255854	16.8553	62.1	284	.2400			
	5.172075	17.1303	29.5	135	.0915			
	5.035719	17.5978	37.0	169	.1200			
	4.978813	17.8006	31.3	143	.0400			
	4.758441	18.6321	40.7	186	.1000			
	4.688853	18.9112	46.0	210	.0915			
	4.577465	19.3757	29.5	135	.0915			
	4.479376	19.8043	35.5	162	.1000			
	4.383704	20.2410	63.6	290	.1200			
	4.246196	20.9037	59.5	272	.1400			
	4.088125	21.7216	19.7	90	.0200			
	3.941748	22.5386	62.9	288	.1400			
	3.778991	23.5229	27.9	128	.0400			
	3.696576	24.0551	30.5	139	.1000			
	3.523769	25.2537	35.6	163	.2400			
	3.459683	25.7295	44.7	204	.0800			
	3.338511	26.6803	28.7	131	.0200			
	3.273450	27.2206	45.5	208	.1000			
	3.135320	28.4446	23.6	108	.0600			
	3.108154	28.6985	25.9	118	.0200			
	3.018687	29.5681	34.4	157	.1400			
	2.923031	30.5589	21.9	100	.0200			
	2.844431	31.4249	18.4	84	.0200			
	2.749393	32.5408	28.5	130	.1200			
	2.713739	32.9804	25.6	117	.0200			
	2.663207	33.6246	19.6	90	.0600			
	2.613490	34.2838	17.4	80	.0200			

What is claimed is:

1. A crystalline salt of 5-methyl-(6R,S)-, -(6S)- or -(6R)-tetrahydrofolic acid said crystalline salt having a water of crystallization of at least one equivalent per equivalent of 5-methyltetrahydrofolic acid.

2. A crystalline salt according to claim 1, of 5-methyl-(6S)- or -(6R)-tetrahydrofolic acid.

3. A crystalline calcium salt according to claim 1, of 5-methyl-(6S)- and -(6R)-tetrahydrofolic acid having $\geqq 3$ equivalents of water.

4. A crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid with 2 theta values of 6.5, 13.3, 16.8 and 20.1 (Type I) said crystalline salt having a water of crystallization of at least one equivalent per equivalent of 5-methyltetrahydrofolic acid.

5. A crystalline calcium salt according to claim 1, of 5-methyl-(6S)-tetrahydrofolic acid with 2 theta values of 5.3, 6.9, 18.7 and 21.1 (Type II).

6. A crystalline calcium salt according to claim 1, of 5-methyl-(6S)-tetrahydrofolic acid with 2 theta values of 6.8, 10.2, 15.4 and 22.5 (Type III).

7. A crystalline calcium salt according to claim **1**, of 5-methyl-(6S)-tetrahydrofolic acid with 2 theta values of 6.6, 15.9, 20.2 and 22.5(Type IV).

8. A method of producing crystalline salts of 5-methyl-(6R,S)-, -(6S)- and 5-methyl-(6R)-tetrahydrofolic acid, comprising subjecting a salt of 5-methyl-(6R,S)-, -(6S)- or -(6R)-tetrahydrofolic acid in a polar medium to a thermal treatment, at a temperature above 60° C., and thereafter crystallizing said salt from the resultant heated solution.

9. A method according to claim **8**, wherein the crystallisation is effected after thermal treatment at a temperature above 85° C.

10. A method according to claim **8**, wherein the crystallisation is effected from a solution.

11. A method according to claim **8**, wherein the crystallisation is effected from a suspension.

12. A method according to claim **10**, characterised in that crystallisation is effected from water or from a mixture of water and an organic solvent which is miscible with water.

13. A method according to claim **8**, wherein said salt is an alkaline earth salt.

14. A method according to claim **8**, wherein said salt is calcium.

15. A method of producing 5-methyl-(6S)-tetrahydrofolic acids with 2 theta values of 5.3, 6.9, 18.7 and 21.1 (Type II) comprising drying sufficiently 5-methyl-(6S)-tetrahydrofolic acid with 2 theta values of 6.5, 13.3, 16.8 and 20.1 (Type I).

16. A method of producing 5-methyl-(6S)-tetrahydrofolic acid with 2 theta values of 6.8, 10.2, 15.4 and 22.5 (Type III) comprising subjecting to sufficient thermal treatment at above 90° C., a crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid with 2 theta values of 6.5, 13.3, 16.8 and 20.1 (Type I).

17. A method of producing 5-methyl-(6S)-tetrahydrofolic acid with 2 theta values of 6.6, 15.9, 20.2, 22.5 (Type IV) comprising subjecting to sufficient thermal treatment at above 95 ° C., a crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid with 2 theta values of 6.5, 13.3, 16.8 and 20.1 (Type I).

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

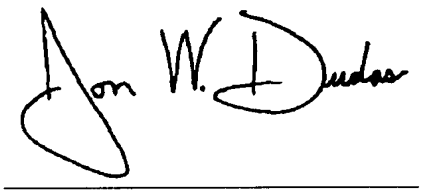
PATENT NO. : 6,441,168 B1
DATED : August 27, 2002
INVENTOR(S) : Rudolf Muller et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 12,
Line 4, reads "acids," should read -- acid --

Signed and Sealed this

First Day of June, 2004



JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

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Maintenance Fee Statement

11/23/2010 11:40 AM EST

Patent Number: 6441168

Customer Number: 000000

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON VA 22201

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The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR-CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,441,168	$900.00	$0.00	02/03/06	09/551,405	08/27/02	04/17/00	04	NO	EPROV-15

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PATENT NUMBER	FEE AMT	SUR-CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,441,168	$2,480.00	$0.00	01/29/10	09/551,405	08/27/02	04/17/00	08	NO	EPROVA AG

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3 mg drospirenone + 0.02 mg ethinyl estradiol (stabilized as Betadex as a clathrate) + 0.451 mg L-5 methyltetrahydrofolate as calcium salt [Metafolin®]

IND 72,287 (YAZ Plus Oral Tablets)

Chron

Type[±]	Description	Date
Other	Guidance Meeting Request – Oral contraceptives supplemented with folate	06/06/05
Corresp. Authority	Metafolin Information	06/09/05
Acknowledgement Letter	FDA refers to the 6/6/05 requesting a meeting for 8/5/05 and includes fax from 6/20/05 granting the meeting	06/20/05
Fax	FDA confirmation for new date of Type C Meeting for 9/8/05	06/29/05
General Correspondence	Type C (Guidance) Meeting Information Package	08/05/05
Fax Letter	Fax received from Charlene Williamson at the FDA for Moo-Jbong Rhee, PhD referring to Bayer's meeting package dated August 5, 2005; Serial Number 002, regarding the guidance meeting for the Metafolin supplemental contraceptives and they have an information request. Letter from Moo-Jhong Rhee, Ph.D at the FDA received at Bayer on September 6, 2005. 8/26/05 referring to Bayer's meeting package dated August 5, 2005; Serial Number 002, regarding the guidance meeting for the Metafolin supplemental contraceptives and they have an information request.	08/26/05
Fax	Fax from Michael Doroshuk, Manager DRA to Ms. Karen Kirchberg at the FDA PIND 72,287 Response to request for CMC Information	08/29/05
Letter	Meeting Minutes from the FDA on 9/8/05	09/08/05
Corresp. Authority	Official Meeting Minutes of 8/8/05	10/07/05
Corresp Authority	PIND 72287 Metafolin supplemental oral contraceptives RE: General Corresp.	10/19/05
Corresp.Authority	PIND 72,287 Metafolin supplemental oral contraceptives Re: General Corresp.	11/22/05
General Correspondence	Type C (Guidance) Meeting Request and Meeting Information Package	12/20/05
Corresp. Authority	IND 72,287 Berlex Dec. 20, 2005 Meeting Request Package	12/21/05
Correspondence Authority	IND 72,287 Berlex Dec 20, 2005	01/06/06
General Correspondence	References to complete the 12/20/05 Type C Meeting Package	01/19/06
Correspondence	PIND 72,287 Metafolin supplemental oral contraceptives	01/19/06

[±] Correspondence Authority = Letter, Fax, Email, phone

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3 mg drospirenone + 0.02 mg ethinyl estradiol (stabilized as Betadex as a clathrate) + 0.451 mg L-5 methyltetrahydrofolate as calcium salt [Metafolin®]

IND 72,287 (YAZ Plus Oral Tablets)

Type±	Description	Date
Authority	Re: General Correspondence: References	
Correspondence Authority	PIND 72,287 Metafolin supplemental oral contraceptives Re: General Correspondence: References	01/19/06
Correspondence Authority	PIND 72,287 Metafolin supplemented oral contraceptives RE: General Correspondence Additional copies of Information Package	01/25/08
Correspondence Authority	Meeting request to take place March 10, 2006 as Type C meeting in reference to December 20, 2005 Correspondence containing the meeting information package and the meeting request.	02/02/06
Correspondence Authority	Meeting request granted to take place March 10, 2008 as Type C meeting	02/03/06
Correspondence Authority	IND 72,287 Berlex Dec. 20, 2005 Meeting Request	02/09/06
Correspondence Authority	Q and A for March 2006 meeting	02/28/06
Email	Email from Sharon Brown to Nita Crisostomo at the FDA.	03/03/06
Correspondence Authority	IND 72,287 Berlex March 10, 2008 Meeting	03/03/06
Email	Email from Sharon Brown to Nita Crisostomo at the FDA.	03/06/06
Correspondence Authority	IND 72,287 Berlex March 10, 2006 Meeting	03/09/06
Email	Email from Sharon Brown to Nita Crisostomo at the FDA.	03/09/06
Correspondence Authority	Metafolin Supplemental Combined Oral Contraceptives Scientific Advice Meeting Minutes	03/10/06
Correspondence Authority	Official meeting minutes	03/10/06
Correspondence Authority	IND 72,287 Berlex March 10, 2006 Mtg.	03/16/06
Email	Email from Sharon Brown to Nita Cristomo at the FDA.	03/17/06
Letter	Meeting Minutes from the FDA on 3/10/06	04/09/06
Correspondence Authority	Berlex	04/11/06
OTHER	Response to April 9, 2006 Meeting Minutes, And request for comments regarding two studies	07/18/06
Correspondence Authority	Berlex Confidential	01/18/07
Correspondence Authority	Berlex Confidential	02/26/07
Initial	Initial New Drug Application **SN 000**	03/01/07

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3 mg drospirenone + 0.02 mg ethinyl estradiol (stabilized as Betadex as a clathrate) + 0.451 mg L-5 methyltetrahydrofolate as calcium salt [Metafolin®]

IND 72,287 (YAZ Plus Oral Tablets)

Type±	Description	Date
Letter	Acknowledgement Letter from Kassandra Sherrod, R.Ph at the FDA that the IND was submitted on March 1, 2007 and received on March 5, 2007.	03/08/07
Correspondence Authority	Acknowledgement of receipt of IND received March 5, 2007	03/08/07
General Correspondence	Company Name Change **SN 001**	04/03/07
Protocol Amendment	New Investigators **SN 002**	07/09/07
Letter	Letter from Scott, Monroe, MD at the FDA received at Bayer on 8/7/07: Request for Information re: IND	08/02/07
Protocol Amendment	Change in Protocol New/Updated Investigators Information, and Change in Outsourcing of Clinical Supplies **SN 003**	08/30/07
Response to FDA Request for Information	Response to FDA Request for Information **SN 004**	10/02/07
Protocol Amendment	(Change in Protocol/New Investigators) Protocol 310662 **SN 005**	11/14/07
Safety Report	Initial Safety Report, MFC#: 200716243NA **SN 006**	01/14/08
Correspondence Authority	Acknowledgement of correspondence of April 2, 2007 of company name change	02/25/08
Letter	Acknowledgement Letter from the FDA regarding Bayer's Name Change	03/03/08
Safety Report	Follow-Up Report, MFC#: 200716243NA **SN 008**	06/13/08
Annual Report	Reporting Period: 03/01/07-02/29/08 **SN 007**	10/22/08
Safety Report	Follow-Up Report, MFC#: 200716243NA **SN 009**	11/07/08
Protocol Amendment	Request for FDA Comment to SAP **SN 010**	11/12/08
Phone	Phone call to obtain the status of the FDA review of the SAP Amendment 4, regarding Protocol 310662 (US Folate Benefit Study) submitted 11/7/08.	11/14/08
Safety Report	Initial Written Report, MFC#: 200812748NA **SN 011**	11/19/08
Phone	Phone call to check on the status Of the Division's review of SAP for Protocol 310662	11/21/08

3 mg drospirenone + 0.02 mg ethinyl estradiol (stabilized as Betadex as a clathrate) + 0.451 mg L-5 methyltetrahydrofolate as calcium salt [Metafolin®]

IND 72,287 (YAZ Plus Oral Tablets)

Type±	Description	Date
Phone	Phone call to follow up on the status of the SAP for Protocol 310662.	11/26/08
Safety Report	Follow-Up #1 to a Written Report, MFC#: 200812748NA **SN 012**	12/02/08
Safety Report	Follow-Up #3 to a Written Report, MFC#: 200716243NA **SN 013**	12/12/08
Email	Inform RPM, Pamela Lucarelli that SN 014 was submitted via the FDA Gateway. This submission contains Bayer's request for a Type B Pre-NDA Meeting	12/18/08
General Correspondence	Request for Pre-NDA Meeting **SN 014**	12/18/08
General Correspondence	Change of US Regulatory Representative **SN 015**	01/07/09
Letter	Letter from Jennifer Mercier of the FDA that Type B Meeting has been scheduled for April 6, 2009 from 10:30 AM-12:00 PM	01/16/09
Protocol Amendment	Protocol Amendment –Change in Protocol **SN 016**	03/03/09
General Correspondence	Pre-NDA Meeting Briefing Package **SN 017**	03/06/09
Email	Email from Pamela Lucarelli at the FDA in response to a voicemail message left by Kavita Johal on Friday 3/6/09 requesting information on the date that preliminary responses to the Pre-NDA Meeting may be expected.	03/09/09
Email	Email to Pamela Lucarelli at the FDA in response to her request for the final attendee list and foreign visitor forms.	03/10/09
Phone	Phone call to Jeannie Roule (FDA) to inquire as to how to obtain an NDA Number for the upcoming YAZ Plus (IND 72,287) submission; J Roule is the Regulatory Project Manager covering for Pam Lucarelli who is on maternity leave	03/19/09
Email	Email to Jeannie Role at the FDA regarding an NDA Number request and call made to David Harrod from the document room.	03/19/09
Email	Email to CDER APPNUMREQUEST at the FDA (Mia Prather and Maureen Cutbert) to request and NDA Number. NDA 22-532 was provided for YAZ Plus.	03/23/09
Email	Email to Jeannie Roule (RPM) at the FDA to inform her of the assigned NDA Number 22-532 from CDER APPNUMREQUEST for the YAZ Plus Submission.	03/23/09
Email	To thank Jeannie Roule (RPM) at the FDA for providing the telephone number and email to the electronic document room so that NDA Number 22-532 was provided for the upcoming YAZ Plus Submission and looking forward to	03/23/09

3 mg drospirenone + 0.02 mg ethinyl estradiol (stabilized as Betadex as a clathrate) + 0.451 mg L-5 methyltetrahydrofolate as calcium salt [Metafolin®]

IND 72,287 (YAZ Plus Oral Tablets)

Type±	Description	Date
	seeing her at the Pre-NDA Meeting.	
Phone	To follow up with Jeannie Roule Regulatory Project Manager (RPM) regarding her email request to provide titles and positions of the Bayer attendees for the April 6, 2009 Pre-Meeting and to inquire about the status of the Division's scheduled internal meeting (March 26, 2009)	03/26/09
Phone	To follow up with the FDA regarding the upcoming Pre-NDA Meeting	04/02/09
Phone	K. Johal of Bayer called J. Roule of the FDA to follow-up regarding the upcoming Pre-NDA	04/02/09
Email	K. Johal emailed Jeannie Roule RPM at the FDA to follow-up on a phone conversation earlier that day regarding cancelling the scheduled pre-NDA Meeting.	04/02/09
Email	Email from K. Johal to Jeannie Roule, RPM at the FDA in follow-up to the preliminary responses to the pre-NDA briefing package submitted on March 6, 2009 to clarify response to NC question #7.	04/13/09
Email	Jeannie Roule, RPM emailed response to K. Johal's inquiry regarding FDA's preliminary response to pre-NDA briefing package (Question #7).	04/13/09
Letter	FDA Letter from Lisa Soule, MD received May 18, 2009 containing preliminary responses to questions presented in the March 6, 2009 pre-NDA meeting briefing package (final version) and clarification of nonclinical summaries (Question #7).	05/11/09
Annual Report	Reporting period of 02/29/08 – 04/03/09 **SN 0018**	06/03/09
Correspondence Authority	RPM Response to emailed clarification re: pre-NDA briefing package, question #7.	07/14/09
Information Amendment	Pharmacology/Toxicology **SN 0019**	07/23/09
Other	Evaluation of Current Safety Date for YASMIN® and Review of British Medical Journal (BMJ) Studies was submitted to the FDA on October 20, 2009. **SN 0020**	10/20/09
Protocol Amendment	New Investigator and Study Site Changes **SN 0021**	12/09/09
Annual Report	Reporting period: 04/04/09 – 04/03/10 **SN 0022**	06/03/10

Yaz Plus
NDA 22-532
Chron Log
August 2009- September 2010

Type	eCTD Sequence	Description	Date
Submission	0000	NDA 22-532 ORIGINAL NEW DRUG APPLICATION (drospirenone 3 mg + ethinyl estradiol 0.02 mg + levomefolate calcium 0.451 mg)	8/21/2009
Email		To FDA alerting them that NDA submission went in through the gateway	8/21/2009
Phone		**FDA Request #1** for NDA - Word version of clean label	8/25/2009
Email		From FDA providing confirmation of receipt of Original NDA, Sequence Number 0000	8/25/2009
Email		Email response to FDA request for Word Version of the label	8/25/2009
		FDA clarification of receipt date for NDA 22-532	8/26/2009
Email		Email containing FDA Acknowledgement letter	8/27/2009
		NDA Acknowledgement letter	8/27/2009
Phone		Phone call to obtain additional information regarding FDA's process for the review of a submission for the Evaluation of Proprietary Names	8/31/2009
		FDA Request #2 regarding clairification on Efficacy SAS datasets for pivotal study	9/23/2009
Submission	0001	NDA 22-532: AMENDMENT eCTD Sequence No. 0001 REQUEST FOR PROPRIETARY NAME REVIEW	9/25/2009
Email		Asked the FDA Drug Registration and Listing Team about the way in which an unapproved drug in finished dosage form could be listed at the FDA under the Pre-Launch Activities Importation Request Procedure	9/25/2009
Phone		Follow-up with FDA regarding the Request for Proprietary Name Review submitted on 09/25/2009 and to provide the RPM with an update of recent discussions had with Jeannie David, PM, Chemistry Review Team	9/29/2009
		FDA Request #3 Email of Bayer's response to FDA's questions as well as updated continuation pages for the Form 356h were provided	9/29/2009
Submission	0002	NDA 22-532: AMENDMENT Revised Form FDA 356h	9/30/2009
Phone		**FDA Request #4** FDA called because they were unable to locate a signed form FDA 356h in the NDA	9/30/2009

Type	eCTD Sequence	Description	Date
Email		Follow up with FDA on discussions from 09/25/2009 and 09/29/2009 regarding the submission for a revised FORM FDA 356h and Request for Proprietary Name Review	09/30/2009
Email		**FDA Request #5** Inquire if there is an exclusivity request included in the current submission	10/01/2009
Email		**FDA Request #6** Email sent providing a copy of the medical reviewers findings regarding hyperlinking issues in the CSR for the study 310662	10/01/2009
Submission	0003	NDA 22-532: AMENDMENT eCTD Sequence No. 0003 Revised Form FDA 356h	10/07/2009
Email		Email responding to FDA request #3-CMC establishment information (FDA Form 356h)-4 additional questions	10/07/2009
Email		Email correspondence providing notification of the Pre Approval Inspection for Bayer's Weimar facility concerning YAZ Plus NDA submission	10/26/2009
		Follow up with FDA on the status of the Request for Proprietary Name Review submitted on 09/25/2009 as an amendment to the Original and to determine whether it would be possible to submit update carton container designs.	11/04/2009
Phone		Follow up from earlier phone call as suggest by Maria Wasilik to discuss how to submit the updated carton containers.	11/04/2009
		FDA Request #7 Filing Communication Letter - Request for Information	11/06/2009
Email		Email sent by FDA with the 74 Day Letter for NDA 22-532	11/06/2009
Fax		FDA Fax received regarding teleconference on November 19, 2009. K Johal made a follow-up call to M Wasilik to discuss.	11/16/2009
Submission	0004	NDA 22-532: AMENDMENT (eCTD Sequence No. 0004) Response to FDA Filing Communication Letter	11/17/2009
Fax		Sent to FDA listing attendees for t-con to be held on November 19, 2009.	11/17/2009
Phone		Follow up with FDA regarding the FDA Fax received on 11/16/2009 requesting a teleconference to discuss the proprietary name review of Yaz Folate	11/17/2009
Email		Email from Pamela Lucarelli of FDA confirming receipt of submission (Sequence 0004)	11/18/2009
Phone		Follow up with FDA regarding the 11/19/2009 teleconference for Yaz Folate tradename	11/18/2009
Email		Confirm FDA's receipt of fax sent on November 17, 2009 and inform them of one additional participant.	11/18/2009
		Executive Summary of FDA Teleconference Re: Yaz Folate Propietary Name prepared by K Johal	11/19/2009
Email		Email between Kavita Johal and Maria Wasilik discussing secure email set up.	11/20/2009
Phone		Follow up with FDA from the November 19, 2009 FDA T-con to discuss Yaz Folate.	11/25/2009

Type	eCTD Sequence	Description	Date
Submission	0005	NDA 22-532: (eCTD Sequence No. 0005) WITHDRAWAL of REQUEST FOR PROPRIETARY NAME REVIEW	12/04/2009
Phone/Email		Summary of voice messages and email to inform FDA of Bayer's submission for the Withdrawal of the Request for Proprietary Name Review	12/04/2009
		Official FDA Meeting Minutes	12/09/2009
Submission	0006	Re: NDA 22-532: AMENDMENT (eCTD Sequence 0006) REQUEST FOR PROPRIETARY NAME REVIEW	12/16/2009
Submission	0007	RE: NDA 22-532 Amendment (eCTD Sequence 0007) 4 Month Safety Update	12/16/2009
Phone		Discussed scheduling of an inspection for NDA 22-532 for the analytical site in the Netherlands	12/17/2009
		Information Request from FDA (Roy Blay, DSI, FDA) needed to scheduled clinical site inspections for NDA 22-523, Study 310662, Sites 108 and 103.	12/17/2009
Letter		Letter for FDA Inspection of PRA International, January 18-22, 2010 for NDA 22-532	12/18/2009
Phone		Follow-up with FDA regarding the letter for the FDA inspection for NDA 22-532 on January 18-22, 2010 at PRA International (analytical site for Studies 309664 and 309662	12/18/2009
Phone		Phone call from Mr. Aisen to introduce himself as the lead investigator for the upcoming inspection at PRA international	12/22/2009
Letter		FDA Letter - Proprietary Name Request Withdrawn	12/29/2009
Letter		Bayer provided PRA letter of confirmation for upcoming inspection	12/29/2009
Phone		Discussed the best and most expeditious means of submitting the updated first user effect data.	01/05/2010
Phone		Discussed with the Supervisory Project Manager the best and most expeditious means of submitting the updated first user effect data	01/05/2010
Email		**FDA Request #8** Email for Information Request from P. Lucarelli requesting clinical pharmacology information.	01/05/2010
Letter		Letter from FDA - PROPRIETARY NAME REQUEST WITHDRAWN dated 12/29/09	01/06/2010
		To follow up on two items after our discussions on January 5 and 6, 2010 regarding how to submit updated first user effect data	01/08/2010
		In follow up to detailed discussions on January 5 and 6, 2010, to clarify two items	01/08/2010
Submission	0008	Response to FDA Information Request #8	01/11/2010
Submission	0009	inform DRUP of the requested information from the Division of Scientific Investigations (Dr. Roy Blay) for clinical site inspections (Study 310662, Sites 103 and 108)	01/21/2010

Type	eCTD Sequence	Description	Date
		To provide the requested information for NDA 22-532, Study 310662, Sites 103 and 108 to Dr. Roy Blay (4 CDs)	01/21/2010
		Form FDA 483 received for the inspection conducted at PRA International (announced on December 17, 2009) for Study 309664	01/22/2010
Email		**FDA Request #9** Email from Pam Lucarelli for Request for Information regarding Clinical Pharmacology Information	01/25/2010
Email		**FDA Request #10** Email from Pam Lucarelli for Request for Information for clinical information for NDA 22-532	01/25/2010
		Letter for FDA Inspection of for NDA 22-532 for Dr. Wouter H. J. Vaes (Study 310662) in the Netherlands, 3/1-5/2010	01/29/2010
		Letter for FDA Inspection of for NDA 22-532 for Dr. Christine Klipping (Study 309664) in the Netherlands, 3/8-12/2010	01/29/2010
		Email: Follow up regarding FDA Inspection of NDA 22-532 for Dr. Christine Klipping (Study 309664) in the Netherlands, 3/8-12/2010	01/29/2010
Submission	0010	AMENDMENT - Response to FDA Information Request (to Request for Information (#9) regarding Clinical Pharmacology Information)	02/03/2010
Letter		FDA Inspection Confirmation Letter for TNO, Dr. Wouter H. J. Vaes in the Netherlands, 3/1-5/2010.	02/03/2010
		Confirmation letter sent to FDA regarding FDA Inspection of NDA 22-532 for Dr. Christine Klipping (Study 309664) in the Netherlands	02/03/2010
Submission	0011	AMENDMENT - Response to FDA Information Request (Request for Information (#10) regarding Clinical Information)	02/04/2010
Email		Email from K. Johal to P. Lucarelli at FDA (re: eCTD 0010)	02/05/2010
Email		Email from L. Carrion to K. Johal re: flight and hotel information for investigator Diane Van Leeuwen for the inspection at TNO	02/11/2010
Email		Email from L. Carrion to K. Johal providing flight and hotel information for the FDA Inspector (Susan Yuscius) for the Inspection of Dinox BV.	02/16/2010
Email		Email from L. Carrion to K. Johal regarding inspection at TNO	02/16/2010
Email		Email from L. Carrion to K. Johal regarding contact information for FDA Inspector, Susan Yuscius, for the Inspection of Dinox BV	02/17/2010
Phone		Phone conversation between K Johal and P. Lucarelli (see contact report)	02/17/2010
Submission	0012	Additional Response to FDA Filing Communication Letter & Submission of Final Report 47012 (Population PK/PD)	03/01/2010
Email		**FDA Request #11** Email from P. Lucarelli for Request for Information for clinical pharmacology information for NDA 22-532	03/02/2010
		Form FDA 483 issued to TNO (bioanalytical lab for studies 309763 and 311642).	03/05/2010

Type	eCTD Sequence	Description	Date
Submission	0013	Submission to FDA in response to Information Request #11 regarding clinical pharmacology	03/11/2010
		Form FDA 483 issued to Dinox BV (bioequivalent clinical site in Netherlands for study 309664, supportive study for NDA 22-532, Yaz Plus).	03/12/2010
Letter		Letter Received from FDA - Proprietary Name Request, Conditionally Accepted	03/16/2010
Phone		**FDA Request #12** P. Lucarelli called to request letter of authorization be sent from PRA International	03/17/2010
Phone		P. Lucarelli called to clarify which inspection and site she was referring to. Ms. Lucarelli clarified that she needed a letter of authorization from PRA International.	03/18/2010
Fax		A Form FDA 483 was issued to Site 103 (Dr. Lyles, Study 310662, US Benefit Study), by Nancy E. Fontaine, dated March 19, 2010, listing observations made during the inspection.	03/19/2010
Email		On March 19, 2010, K. Johal sent P. Lucarelli a Letter of Authorization for PRA International per Ms. Lucarelli's email request on 3/18/10.	03/19/2010
		In response to P. Lucarelli's email request (dated 3/22/10) that the Letter of Authorization is sufficient and should be submitted, K. Johal responded later that day to let her know that it was submitted to the NDA [eCTD Sequence No. 0014] and attached the cover letter for her reference.	03/22/2010
Submission	0014	Response to FDA Request: Letter of Authorization from PRA International	03/22/2010
Email		**FDA Request #13** Email from P. Lucarelli for Request for Information for clinical pharmacology information	03/30/2010
Letter		**FDA Request #14** Dinox Response Letter to Form FDA 483, Inspection Observations (Study 309664)	03/30/2010
Letter		General Advice Letter received from FDA re: finding of the PRA Inspection (Received by mail on April 7, 2010)	03/31/2010
Phone		P. Lucarelli called before sending the attached email (Division's response to the request for clarification for FDA Recommendation #2 in the General Advice Letter received by email on April 1, 2010).	04/07/2010
Email		K. Johal sent an email to P. Lucarelli on April 8, 2010 to ask for clarification of one of the Division's recommendations included in the General Advice Letter (see contact report dated 4/1/10) based on findings of the FDA DSI inspection of PRA International Group BV regarding the bioanalysis of samples from Study 309554.	04/08/2010
		FDA Request #15 CMC Request for Information	04/09/2010
Submission	0015	Submission (eCTD Sequence 0015) - Response to FDA Information Request (Request for Information #13 regarding Clinical Pharmacology)	04/16/2010
		Form FDA 483 was issued to Anapharm, Inc. (Johane Boucher-Champagne, President and CEO), by Investigator Martin K. Yau, PhD, on April 16, 2010. Observations made during the inspection on April 5-8, 2010 pertain to studies	04/16/2010

Type	eCTD Sequence	Description	Date
		309662 and 309664 sponsored by Bayer Schering Pharma which has been submitted in support of NDA 22-532 (Beyaz).	
Phone		Two conversations with Ms. Lucarelli on 4/14/2010 and 4/19/2010. The main purpose of Ms. Lucarelli's calls was to find out the status of our responses to the pending information requests for NDA 22-532 (Beyaz), most importantly, to the General Advice Letter. Request 1: Clin Pharm request received by email on 3/30/2010, submission was made on 4/16/2010. Request 2: General Advice Letter (main reason for the phone call) the request involves conducting new analyses and preparing an amended report which is what is taking some time (planned to submit on May 7, 2010) Request 3: CMC request for information (#15). This request was referring to the Day 74 letter and contained the same question for which we had responded.	04/19/2010
E-mail		K. Johal sent an email to P. Lucarelli providing information available in response to the Division's General Advice Letter (see Contact Report distributed on April 1, 2010). The email contained the Division's recommendations and Bayer's preliminary responses and/or questions for clarification.	04/20/2010
Submission	0016	A response to the FDA's information request dated April 9, 2010 (#15) was submitted. The Agency requested that we provide the names and addresses of the manufacturers of the primary packaging material (blister packs), along with letters of authorization for the drug master files for the materials. This submission includes the requested information. The request also included the same question as the 74-day letter regarding the age of the clinical supplies used. Our response included a re-iteration of the previously supplied response to the 74-day letter.	04/22/2010
Submission	0017	Response to FDA Information Request submission was made to the FDA, Sequence No. 0017 via Gateway, in response to the Division's General Advice Letter (Request #14).	04/23/2010
Phone		P. Lucarelli (FDA) called to follow up regarding response to the General Advice Letter, and inquired when the formal submission would be made and discussed the timeline (extension TBD after the submission, approximately 2 weeks after, before the PDUFA goal date).	04/23/2010
Letter		Form FDA 483 was issued to William D. Koltun, MD (Principal Investigator, Study 310662), by Investigator Yvette E. Guillermo, on April 23, 2010. Observations made during the inspection on April 13-23, 2010 pertain to study 310662 sponsored by Bayer Schering Pharma which has been submitted in support of NDA 22-532 (Beyaz).	04/23/2010
E-mail		P. Lucarelli sent an email to K. Johal which included clarification to FDA Recommendation #4 (Request #14) of the General Advice Letter in response to Bayer's preliminary responses/questions.	04/26/2010
E-mail		K. Johal sent an email to P. Lucarelli requesting clarification to Recommendation #3 of the General Advice Letter.	05/04/2010

Type	eCTD Sequence	Description	Date
E-mail		K. Johal sent a Response to Recommendation #4 in the General Advice Letter, via email, in advance of the electronic submission scheduled for May 7, 2010.	05/05/2010
E-mail		K. Johal sent an email to Jeannie Roule of FDA (RPM covering for Pam Lucarelli while on vacation) to inform her that she will be out of the office on May 6th, 7th and 10th and to please copy S. Brown on any correspondence regarding IND 73,518 and/or NDA 22-532.	05/05/2010
Letter		William D. Koltun, MD (Principal Investigator participating in Study 310662 in support of NDA 22-532) sent the FDA a response to the Form FDA 483 (issued on 4/23/2010) for the inspection conducted on April 13-23, 2010 of the study records of the participating clinical study site.	05/06/2010
Phone		Ms. Roule asked about submission 0018 (scheduled to be submitted through the FDA Gateway by 4:30). The cover letter was sent via e-mail.	05/07/2010
Submission	0018	Response to FDA Information Request submission was made to the FDA, Sequence No. 0018 via Gateway, in response to the Division's General Advice Letter (Request #14).	05/07/2010
Email		J. Roule confirmed via email receipt of the Response to FDA Information Request (Request for Information #14) (eCTD Sequence 0018), in response to S. Brown's email letting her know that the submission had been sent through, and inquired whether she should expect any additional information to be submitted. S. Brown responded with confirmation that the submission is complete.	05/10/2010
Letter		A Review Extension - Major Amendment Letter was received from FDA. The extended user fee goal date is September 24, 2010.	05/11/2010
Phone		P. Lucarelli called and stated the following: • Review extension: to September 24, 2010. • NDA 22-532 would not be a NME (NDA 22-574 Yasmin Plus would be. • Everything submitted to NDA 22-532 must be cross-referenced to NDA 22-574 (Yasmin Plus). • The Division may address labeling for Beyaz first and then ask us to apply the comments to NDA 22-574 (Yasmin Plus) or vice versa (comments should be the same). DMEPA has made comments and the revised labeling should be sent back once the changes have been made. • "Beyaz" has already been approved, pending final approval of the product. • Comments on the packaging would be sent by the end of the week, because she needed to give them to the CMC Reviewer. (Please note: Ms. Lucarelli emailed comments on carton/container labeling for Beyaz on May 19, 2010). • Tadename submission: she had received a voice message from Bob Haydu regarding NDA 22-574 indicating that the submission had been delayed.	05/18/2010

Type	eCTD Sequence	Description	Date
Email		**FDA Request #16** P. Lucarelli emailed a Request for Information re: letter from PRA.	05/18/2010
Email		This contact report applies to NDA 22-532 (Beyaz) and NDA 22-574 (Yasmin Plus). The email clarifies the Division's plans regarding the action dates for the Beyaz and Yasmin Plus NDAs. The Division will take action on NDA 22-574 (Yasmin Plus) first.	05/18/2010
Email		**FDA Request #17** P. Lucarelli emailed a list of comments for the proposed container/carton labeling. Note: The container/carton labeling will not be considered final until approval (PDUFA goal date: September 24, 2010)	05/19/2010
Email		K. Johal sent an email to P. Lucarelli in response to FDA request #17 (emailed on May 19, 2010) seeking the Division's feedback on the proposed carton/container label prior to submission to FDA.	05/24/2010
Submission	0019	Response to FDA Information Request submission [Sequence No. 0019] was made, in response to the Division's email dated May 18, 2010 (Request for Information #16, see contact report dated 5/18/10).	05/27/2010
Phone		Called P. Lucarelli re: the status of the Division's review of our proposal and to request feedback prior to submission. Also discussed request for exclusivity which Ms. Lucarelli stated she would speak Jen Mercier (Supervisory Project Manager).	05/28/2010
Email		P. Lucarelli responded to K. Johal's email providing comments regarding the revised foil (sent via email on May 24, 2010).	06/01/2010
Phone		P. Lucarelli clarified the timeframe for the actions of the two NDAs, the action for Yasmin Plus cannot be taken before Beyaz because the data lie in the Beyaz application. Ms. Lucarelli mentioned the possibility of a clock extension for Yasmin Plus and noted that a Tradename (Calyova) submission had been made. Ms. Lucarelli confirmed sending additional comments on the foil and K Johal stated the revised foil was sent by email in the morning addressing all comments and indicated a formal submission will be made. K. Johal asked if the CMC Reviewer could review the revised foil to ensure that all comments have been adequately addressed and Ms. Lucarelli stated that she would be able to do this.	06/07/2010
Email		K. Johal sent the updated Beyaz Trade Foil incorporating the Division's comments to P. Lucarelli via email.	06/07/2010
Email		P. Lucarelli responded to K. Johal's June 7, 2010 email by providing further comments regarding the updated foil.	06/08/2010
Email		K. Johal resent a revised Beyaz Trade Foil incorporating the Division's comments to P. Lucarelli via email.	06/09/2010
Email		Pam Lucarelli replied to email from June 9, 2010 which contained a revised trade foil with FDA's comments incorporated.	06/11/2010
Email		K. Johal sent a revised Beyaz Carton/Container Labeling incorporating the Division's comments (received on 5/19/10) to P. Lucarelli via email.	06/15/2010
Email		P. Lucarelli sent clarification regarding the use of the TM and, additionally, requests the strength be included on the back of	06/15/2010

Type	eCTD Sequence	Description	Date
		the foil.	
Email		P. Lucarelli sent comments regarding the Beyaz Carton/ Container.	06/16/2010
Email		**FDA Request #18** P. Lucarelli emailed an Information Request: • An assessment of the impact, if any, of levomefolate calcium on the safety and efficacy of Beyaz for the treatment of acne vulgaris and premenstrual dysphoric disorder (PMDD) • Final reports of any studies conducted to characterize the safety and efficacy of the proposed combination product for the treatment of acne vulgaris and PMDD	06/24/2010
Email		K. Johal sent updated Beyaz Carton/Container Labeling and responses to the Division's comments (received on 6/16/10) to P. Lucarelli via email.	06/24/2010
Phone		**FDA Request #19** Pam Lucarelli called on 6/29 and requested a letter of authorization be provided from TNO Quality of Life	06/29/2010
Letter		**FDA Request #20** Receipt of FDA Letter entitled General Advice Letter (dated April 15, 2010) for clinical pharmacology comments.	06/29/2010
Submission	0020	Response to FDA Information Request submission [Sequence No. 0020] was made, re: Letter of Authorization for TNO Quality of Life in response to the request from P. Lucarelli of FDA (phone conversation date June 29, 2010) and included the Letter of Authorization (provided by email on July 1, 2010).	07/02/2010
Email		K. Johal emailed a response to FDA request #18, including a request for clarification to P. Lucarelli.	07/02/2010
Email		P. Lucarelli confirmation that the Beyaz Carton sent to the Division by email on 6/24/10 (see contact report issued 6/25/10) looks sufficient. K. Johal replied that Bayer will submit the revised foil and carton/container labeling to the NDA.	07/02/2010
Email		**FDA Request #21** FDA requested that Bayer submit a revised Calyova and Beyaz label to mirror Natazia	07/08/2010
Submission	0021	Response to FDA Information Request submission [Sequence No. 0021] was made, re: carton/container labeling in response to the request from P. Lucarelli of FDA via email on May 19, 2010.	07/09/2010
Email		Emailed the updated draft package insert to P. Lucarelli prior to the formal submission in response to the Division's phone request on July 8, 2010 that Bayer submit a revised Calyova and Beyaz label to mirror Natazia.	07/13/2010
Submission	0022	Response to FDA Information Request submission [Sequence No. 0022] was made re: Revised Draft Package Insert in response to the request from P. Lucarelli of FDA via a telephone conversation on July 8, 2010 requesting revised draft labeling for NDA 22-252 and NDA 22-574. It was requested that Bayer revise the draft labeling to reflect where applicable, the final package insert for Natazia™ (estradiol valerate and estradiol valerate/dienogest) tablets NDA 22-252.	07/14/2010
Submission	0023	Response to FDA Information Request submission [Sequence No. 0023] was made re: an assessment of the impact of	07/15/2010

Type	eCTD Sequence	Description	Date
		levomefolate calcium on the indication of moderate acne vulgaris and the indication of PMDD in response to the request from P. Lucarelli of FDA via a telephone conversation (July 6, 2010) requesting a literature review.	
Submission	0024	Response to FDA Information Request submission [Sequence No. 0024] was made re: clinical pharmacology comments in response to a General Advice Letter (April 15, 2010) requesting information regarding Clinical Study Report A34010 (TNO Report V7430/01 and V7430/02).	07/16/2010
Phone		**FDA Request #22** P. Lucarelli requested for Bayer to revise the dissolution method for the Yasmin Plus (proposed proprietary name Calyova) and Beyaz tablets.	07/29/2010
Phone		Phone call between Robert Haydu and Pamela Lucarelli: to confirm receipt of Bayer's email response to FDA's request to revise the dissolution method for the Yasmin Plus tablets. P. Lucarelli then requested a Letter of Authorization from PRA International to be emailed; then shared that FDA would not be able to provide feedback on the proposed labeling for NDA 22-574 by August 9th as stated in the 74-Day letter and be delayed until at least the week of August 16th. She did say that FDA is planning to provide feedback on the proposed labeling for Beyaz (NDA 22-532) next week most likely August	08/06/2010
Email		P. Lucarelli sent an email to R. Haydu and K. Johal communicating that Bayer's response (emailed on July 30, 2010) to FDA's July 26, 2010 email request for Bayer to revise the dissolution method (both Yaz Plus and Yasmin Plus are sufficient and the response can be formally submitted to both applications.	08/06/2010
Submission	0025	Response to FDA Information Request submission [Sequence No. 0025] was made in response to an email dated August 6, 2010 from P. Lucarelli to Robert Haydu indicating the emailed response (July 30, 2010) to the Division's request regarding dissolution method and specifications was considered sufficient and requested it to be submitted formally to both applications, NDA 22-532 and NDA 22-574.	08/09/2010
Email		A Pre-Launch Activities Importation Request (PLAIR) was submitted to FDA to seek FDA authorization to import blistered Beyaz Tablets in bulk in anticipation of the FDA approval of NDA 22-532 (user fee goal date September 24, 2010).	08/09/2010
Phone		Follow-up with Pam Lucarelli regarding status of review of responses to information requests for Beyaz and anticipated receipt of Division's comments on labeling	08/10/2010
Email		Sent to P. Lucarelli requesting that a call be made to Bayer when she is ready to send the labeling for NDA 22-532 and provided P. Lucarelli with coverage information while K. Johal is out of the office (8/12 through 8/16).	08/11/2010
Email		CDER-OC-PLAIR Team confirmed receipt of the Pre-Launch Activities Importation Request (PLAIR) for Beyaz Tablets submitted to FDA on August 9 seeking FDA authorization to import blistered Beyaz Tablets in bulk in anticipation of the FDA approval of NDA 22-532. The CDER-OC-PLAIR Team stated that they would provide their response after they have	08/12/2010

Type	eCTD Sequence	Description	Date
		reviewed the PLAIR.	
Email		Email sent to P. Lucarelli re: labeling. P. Lucarelli will be out of the office until August 19th and didn't anticipate that the labeling will be sent prior to her return to the office.	08/13/2010
Email		**FDA Request #23** P. Lucarelli sent an email to both Robert Haydu and Kavita Johal informing them that an updated dissolution specification sheet was not included in the recent submissions NDA 22-532 and NDA 22-574 and requested that one be submitted. K. Johal replied to P. Lucarelli that an updated dissolution specification sheet will be submitted for both NDAs as soon as possible.	08/20/2010
Phone		Left a voice message with Pam Lucarelli inquiring as to whether she still anticipated sending the labeling for Beyaz (NDA 22-532) to us tomorrow (August 24th) as previously discussed.	08/23/2010
Email		Notification that FDA granted authorization of the PLAIR for Beyaz Tablets.	08/23/2010
Submission	0026	Response to FDA Information Request [eCTD Sequence 0026] was made in response to an emal dated August 20, 2010 from P. Lucarelli to Kavita Johal and Robert Haydu requesting that Bayer provide to NDA 22-532 and NDA 22-574 the updated dissolution specification sheet for the levomefolate tablets.	08/24/2010
Phone		FDA follow-up regarding the status of the Division's comments on the labeling for Beyaz (NDA 22-532)	08/24/2010
Email		Provided the Import Operations and Policy Branch with the Entry Number under which the blistered Beyaz Tablets in bulk is anticipated to arrive at the NY Port of Entry via Newark Liberty International Airport on September 10, 2010, pursuant to the PLAIR enforcement discretion granted by FDA on August 23.	08/24/2010
Phone		Discussion with FDA regarding the submisssion of Bayer's response to the August 20, 2010 information request for NDA 22-574 (Yasmin Plus)	08/26/2010
Fax		Sent to Stella Notzon at the Import Operations and Policy Branch to confirm the Branch's receipt of the Entry Number under which the blistered Beyaz Tablets in bulk is anticipated to arrive at Newark Liberty International Airport on September 10, 2010, pursuant to the PLAIR authorization granted by FDA on August 23.	08/30/2010
Submission		A Provisional Drug Listing, which is a set of the Structured Product Labeling files, for Beyaz was submitted via the FDA gateway to register the National Drug Code (NDC) for bulk blisters scheduled for import into the US on 10Sep10.	09/01/2010
Email		Stella Notzon, Import Operations and Policy Branch [IOP], informed me that on 8/25/2010 the FDA-New York District was advised of the shipment of Beyaz Tablets that will arrive at Newark Liberty International Airport on September 10, 2010, pursuant to the PLAIR authorization, and that no further action is required from IOP.	09/01/2010

Type	eCTD Sequence	Description	Date
Phone		Follow-up with FDA regarding status of Beyaz label (NDA 22-532). P. Lucarelli stated that there have been some developments and the label would be delayed for a few more days, and that there may be an issue with the wording of the indication with metafolin.	09/02/2010
Phone		P. Lucarelli indicated that she would be sending the Division's working copy of the label in track change mode. She stated that we should accept any track changes that we agree with and add any comments, as needed.	09/03/2010
Email		In follow up to the transmission to FDA on 01 Sep 2010 of the provisional drug listing of bulk blisters of Beyaz Tablets pursuant to the PLAIR Authorization, the DRLS Team was provided with a copy of the FDA PLAIR Authorization for Beyaz Tablets, and a copy of the applicable FDA gateway receipt dated 01 Sep 2010 associated with the transmission to FDA of the provisional the drug listing of the bulk blisters of Beyaz Tablets.	09/08/2010
Phone		Bayer follow-up on status of response to the Division's comments (September 3, 2010) on the Beyaz label.	09/09/2010
Email		Email to FDA - Bayer's response to the Division's comments on the proposed label	09/09/2010
Email		Confirmation of receipt of Bayer's response to the Division's comments on the proposed label	09/10/2010
Phone		Follow-up on status of Beyaz label: P. Lucarelli stated that the revised Beyaz label would be sent today, and that she does not have any additional information to disclose regarding the indication and that this will be in the label.	09/16/2010
Email		From P. Lucarelli containing the Division's comments to the Beyaz proposed label. Ms. Lucarelli asks that Bayer respond via email by noon on Monday, 9/20.	09/16/2010
Email		Sent an email to P. Lucarelli containing Bayer's responses to the Division's comments to the Beyaz proposed label.	09/19/2010
Email		**FDA Request #24** P. Lucarelli sent an information request to understand the decrement in plasma folate in the elimination phase in Study A39814.	09/20/2010
Phone		Follow up with FDA regarding FDA information request and receipt of labeling response emailed on 9/18/2010	09/20/2010
Email		P. Lucarelli confirmed receipt of the response to the information request of 9/20/10.	09/21/2010
Email		An information request was emailed to K. Johal from P. Lucarelli. Later the same day, a reply was emailed to P. Lucarelli with answers to the Division's questions regarding labeling.	09/21/2010
Email		Email correspondence: J. Mercier emailed the FDA proposed label to K. Johal	09/22/2010
Email		Email correspondence: Information Request from P. Lucarelli re: revision/addtion of figures to Section 14.4 of the Beyaz label	09/22/2010

Type	eCTD Sequence	Description	Date
Submission	0027	Response to FDA Information Request [eCTD Sequence 0027] change in classification of the application and submission of a requested article for the US Preventative Task Force recommendation	09/23/2010
Email		Email correspondence: Information Request from P. Lucarelli re: revision/addition of figures to Section 14.4 of the Beyaz label and response.	09/23/2010
Email		Email Correspondence: J. Mercier emailed the FDA proposed Beyaz label to K. Johal. K. Johal emailed the response attaching the revised (clean and annotated) Beyaz label.	09/23/2010
Email		Email correspondence: Information Request and Response of requested figures and footnotes.	09/23/2010
Advertising		Advertisement/Promotional Labeling Materials (Press Release)	09/24/2010
Email		NDA Approval Letter (original received in the mail 9/30/10)	09/24/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022532

NDA APPROVAL

Bayer HealthCare Pharmaceuticals Inc.
Attention: Kavita Johal, Pharm.D.
Assistant Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045

Dear Ms. Johal:

Please refer to your New Drug Application (NDA) dated August 21, 2009, received August 24, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium and levomefolate calcium) tablets.

We acknowledge receipt of your amendments dated September 25 and 30, October 7, November 17, and December 4 and 16 (2), 2009, January 11 and 21, February 3 and 4, March 1, 11 and 22, April 16, 22 and 23, May 7 and 27, July 2, 9, 14, 15 and 16, August 9 and 24, and September 23, 2010.

This new drug application provides for the use of Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium and levomefolate calcium) tablets for the following indications:

- Prevention of pregnancy;
- Treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception;
- Treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche;
- In women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is

identical to the enclosed labeling text for the package insert. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on July 9, 2010, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022532.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pre-menarcheal patients because pre-menarcheal patients are not at risk of becoming pregnant and the use of this product before menarche is not indicated. We note that you have fulfilled the pediatric study requirement for post-menarcheal pediatric patients by extrapolation of adult data.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Pamela Lucarelli, Regulatory Health Project Manager, at (301) 796-3961.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Content of Labeling